PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 49/00 — A1

(11) International Publication Number: WO 93/17718

(43) International Publication Date: 16 September 1993 (16.09.93)

(21) International Application Number: PCT/GB93/00470

(22) International Filing Date: 5 March 1993 (05.03.93)

(30) Priority data:
9204918.8 6 March 1992 (06.03.92) GB
9204920.4 6 March 1992 (06.03.92) GB

(71) Applicant *(for all designated States except US)*: NYCOMED IMAGING A/S [NO/NO]; Nycoveien 2, P.O. Box 4220 Torshov, N-0401 Oslo 4 (NO).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : KLAVENESS, Jo [NO/NO]; Midtåsen 5, N-1166 Oslo (NO). REDFORD, Keith [GB/NO]; Seljeveien 3A, N-1481 Hagan (NO). RONGVED, Pål [NO/NO]; Hovdens vei 13, N-1454 Hellvik (NO). SOLBERG, Jan [NO/NO]; Syd-Fossum 43, N-1343 Eiksmarka (NO). STRANDE, Per [NO/NO]; Nordengveien 78A, N-0755 Oslo 7 (NO). WIGGEN, Unni, Nordby [NO/NO]; Vestaveien 11, N-1476 Rasta (NO).

(74) Agent: MARSDEN, John, Christopher; Frank B. Dehn & Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).

(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: IMPROVEMENTS IN OR RELATING TO CONTRAST AGENTS

(57) Abstract

Contrast agents comprising gas-containing or gas-generating polymer microparticles and/or microballoons, in which the polymer is a biodegradable polymer containing units of formula -[-$(O)_m$-CO-O-C(R^1R^2)-O-CO-$(O)_n$-]- (wherein R^1 and R^2 each represent hydrogen or a carbon-attached monovalent organic groups or together form a carbon-attached divalent organic group, and m and n are each independently zero or one) may be used in diagnostic applications such as ultrasounds and MR imaging.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SK	Slovak Republic
CI	Côte d'Ivoire	KZ	Kazakhstan	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
CS	Czechoslovakia	LK	Sri Lanka	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	UA	Ukraine
DK	Denmark	MG	Madagascar	US	United States of America
ES	Spain	ML	Mali	VN	Viet Nam
FI	Finland	MN	Mongolia		

"Improvements in or relating to contrast agents"

This invention relates to novel contrast agents, more particularly to new gas-containing or gas-generating contrast agents of use in diagnostic imaging.

It is well known that ultrasonic imaging comprises a potentially valuable diagnostic tool, for example in studies of the vascular system, particularly in cardiography, and of tissue microvasculature. A variety of contrast agents has been proposed to enhance the acoustic images so obtained, including suspensions of solid particles, emulsified liquid droplets, gas bubbles and encapsulated gases or liquids. It is generally accepted that low density contrast agents which are easily compressible are particularly efficient in terms of the acoustic backscatter they generate, and considerable interest has therefore been shown in the preparation of gas-containing and gas-generating systems.

Initial studies involving free gas bubbles generated in vivo by intracardiac injection of physiologically acceptable substances have demonstrated the potential efficiency of such bubbles as contrast agents in echocardiography; such techniques are severely limited in practice, however, by the short lifetime of the free bubbles. Interest has accordingly been shown in methods of stabilising gas bubbles for echocardiography and other ultrasonic studies, for example using emulsifiers, oils, thickeners or sugars, or by entraining or encapsulating the gas or a precursor therefor in a variety of polymer systems, e.g. as porous gas-containing polymer microparticles or as gas "microballoons" encapsulated by polymer coatings.

Thus, for example, WO 80/02365 discloses the use of gelatin encapsulated gas microbubbles for enhancing ultrasonic images. Such microbubbles do not, however, exhibit adequate stability at the dimensions preferred for

use in echocardiography (1-10 μm) in view of the extreme thinness of the encapsulating coating.

US-A-4774958 discloses the use of microbubble dispersions stabilised by encapsulation in denatured protein, e.g. human serum albumin. Such systems permit the production of microbubble systems having a size of e.g. 2-5 μm but still do not permit efficient visualisation of the left heart and myocardium. The use of such protein-derived agents may also create problems with regard to potential allergenic reactions.

EP-A-0327490 discloses, inter alia, ultrasonic contrast agents comprising a microparticulate synthetic biodegradable polymer containing a gas or volatile fluid (i.e. having a boiling point below 60°C) in free or bonded form. Representative synthetic biodegradable polymers include polyesters of hydroxy carbonic acids, polyalkyl cyanoacrylates, polyamino acids, polyamides, polyacrylated saccharides and polyorthoesters.

Similar biodegradable microparticulate polymers, based on polymerised aldehydes, are described in EP-A-0441468, while systems based on microparticulate poly (amino acid) - poly (cyclic imide) derivatives are described in EP-A-0458079.

EP-A-0458745 discloses air or gas-filled microballoons in which the encapsulating material is a deformable and resilient interfacially deposited polymer which is preferably biodegradable, examples including polysaccharides, polyamino acids, polylactides, polyglycolides, lactide/lactone copolymers, polypeptides, proteins, polyorthoesters, polydioxanone, poly-β-aminoketones, polyphosphazenes, polyanhydrides and poly (alkyl cyanoacrylates). The microballoons are normally prepared by emulsion techniques leading to deposition of the polymer around droplets of a volatile liquid which is subsequently evaporated.

In WO 91/12823 there are described ultrasound contrast agents comprising gas- or vapour-filled polymer microcapsules; preferred polymers include insolubilised

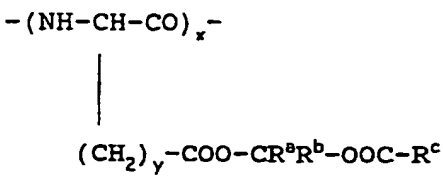
proteins such as denatured albumin. The microcapsules may be prepared by forming a protein shell around a solid or liquid core (e.g. by methods using simple or complex coacervation, double emulsion or minimisation of solubility at isoelectric point), hardening the shell (e.g. by chemical or heat treatment), and removing the core (e.g. by sublimation or evaporation). The use of double emulsion techniques will provide microcapsules having a honeycomb structure with multiple gas- or vapour-filled chambers.

Gas-containing contrast media are also known to be effective in magnetic resonance (MR) imaging, e.g. as susceptibility contrast agents which will act to reduce MR signal intensity. Oxygen-containing contrast media also represent potentially useful paramagnetic MR contrast agents.

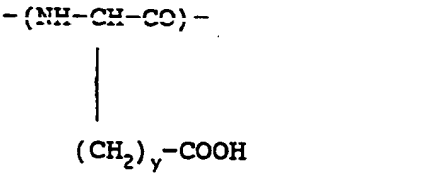
Furthermore, in the field of X-ray imaging it has been observed that gases such as carbon dioxide may be used as negative oral contrast agents.

It is generally acknowledged that polymer-based contrast agents should desirably be biodegradable in order to facilitate their ultimate elimination from or absorption by the test subject. Little attention has been given, however, to the specific design of polymers to maximise this objective, reliance generally being made on the inherent, albeit slow, biodegradability of polymers such as polyesters, polyanhydrides, polycarbonates, polyamides and polyurethanes which principally results from the susceptibility of ester, amide or urethane groups therein to enzymic hydrolysis.

One exception occurs in EP-A-0458745, which suggests the use as ultrasound contrast agents of, inter alia, a specific category of esterified polypeptide derivatives reported to exhibit controlled biodegradability. These polymers, which are described in EP-A-0130935 as delayed release carriers for drugs, comprise compounds of formula



(in which R^a and R^b are alkyl groups or hydrogen atoms and R^c is an optionally substituted aliphatic or aromatic group or R^b is a hydrogen atom or an alkyl group and R^a and R^c together form a divalent group such as a dimethylene, vinylene or phenylene group, y is 1 or 2, and x is such that the molecular weight of the polymer is at least 5000) and copolymers thereof with other poly (amino acids). The first step in the biodegradation of such polymers is said to be cleavage of the side chain methylene diester groups to yield polymers containing units of formula



It is stated that such polymers will then be further degraded by peptidases to their component amino acid(s), which may be absorbed by the host to which the polymer/drug combination was administered, an inherently slow process. Furthermore, the peptide structures may be capable of causing allergenic reactions.

There is thus a continuing need for polymer-based contrast agents which combine the properties of good storage stability, stability <u>in vivo</u> upon administration, preferably for at least several passages of circulation in the case of intracardiac injections, and rapid biodegradation thereafter.

The present invention is based on our findings that these objectives may be fulfilled by contrast agents based on polymers containing methylene diester groups of the

formula (I)

$$\dagger CO\text{-}O\text{-}C(R^1R^2)\text{-}O\text{-}CO \ddagger \qquad (I)$$

(where R^1 and R^2 each represent a hydrogen atom or a carbon-attached monovalent organic group or R^1 and R^2 together form a carbon-attached divalent organic group). Such units are particularly rapidly degraded by common esterase enzymes but are stable in the absence of enzymes. They may be attached not only to carbon-attached organic groups as in simple carboxylate esters but also to -O- atoms as in carbonate esters.

Polymers of this type and a variety of methods for their preparation are described and claimed in our copending International Patent Application No. WO 92/04392, the contents of which are incorporated herein by reference. The units of formula (I) in such polymers may, for example, be present in the polymer backbone, either as repeating units or as linking units between polymer sections, or may be present in crosslinking groups between polymer chains.

A further class of polymers of this type and methods for their preparation are described and claimed in a copending application of even date and comprise non-crosslinked polymers of low or zero water-solubility having a non-polypeptide polymer backbone carrying side chains, at least a proportion of the said side chains containing lipophilic moieties bonded to the polymer backbone by way of methylene diester units of formula (I), whereby the said lipophilic moieties are biodegradatively cleavable to yield a water-soluble polymer.

Thus according to one aspect of the present invention there are provided contrast agents comprising gas-containing or gas-generating polymer microparticles and/or microballoons, characterised in that the polymer is a biodegradable polymer containing units of formula (II)

$$\dagger (O)_m\text{-}CO\text{-}O\text{-}C(R^1R^2)\text{-}O\text{-}CO\text{-}(O)_n \ddagger \qquad (II)$$

(wherein R^1 and R^2 are defined above and m and n, which may be the same or different, are each zero or 1).

Polymers having units of formula (II) in which one or both of n and m are 1, i.e. containing carbonate ester groups, have not previously been proposed other than in WO 92/04392 referred to above, and may be particularly readily biodegradable in some cases.

Polymers having a polypeptide backbone may give unwanted allergenic reactions and in general non-polypeptide polymers are preferred.

Polymers useful used in accordance with the invention may contain units of the formula (III)

$$\{(O)_m\text{-}CO\text{-}O\text{-}C(R^1R^2)\text{-}O\text{-}CO\text{-}(O)_n\text{-}R^3\} \qquad (III)$$

where R^1, R^2, m and n have the above meanings and R^3 is a divalent organic grouping, e.g. a carbon-attached divalent organic grouping.

Such polymers may comprise a plurality of units of formula (III) having different meanings for m, n, R^1, R^2 and R^3, for example as in block or graft copolymers. The diester linkages may occur at intervals throughout the polymer, e.g. as crosslinking groups or between copolymer sections, in which case R^3 will represent a polymeric grouping. Alternatively the linkages may be present throughout substantially the whole of the polymer, in which case R^3 will preferably be a low molecular weight grouping.

Particularly interesting units (III) are those in which m is 0 and n is 0 or 1, i.e. dicarboxylate units of the formula (IV)

$$\{CO\text{-}O\text{-}C(R^1R^2)\text{-}O\text{-}CO\text{-}R^3\} \qquad (IV)$$

or carboxylate-carbonate units of the formula (V)

$$\{CO\text{-}O\text{-}C(R^1R^2)\text{-}O\text{-}CO\text{-}O\text{-}R^3\} \qquad (V)$$

R^1 and R^2 may, for example, each by hydrogen or a

carbon-attached hydrocarbyl or heterocyclic group, for example having 1-20 carbon atoms, e.g. an aliphatic group such as an alkyl or alkenyl group (preferably having up to 10 carbon atoms), a cycloalkyl group (preferably having up to 10 carbon atoms), an araliphatic group such as an aralkyl group (preferably having up to 20 carbon atoms), an aryl group (preferably having up to 20 carbon atoms) or a heterocyclic group having up to 20 carbon atoms and one or more heteroatoms selected from O,S and N. Such a hydrocarbyl or heterocyclic grouping may carry one or more functional groups such as halogen atoms or groups of the formulae $-NR^4R^5$, $-CONR^4R^5$, $-OR^6$, $-SR^6$ and $-COOR^7$, where R^4 and R^5, which may be the same or different, are hydrogen atoms, acyl groups, or hydrocarbyl groups as defined for R^1 and R^2; R^6 is a hydrogen atom or an acyl group or a group as defined for R^1 or R^2 and R^7 is a hydrogen atom or a group as defined for R^1 or R^2. Where R^1 and R^2 represent a divalent grouping this may, for example, be an alkylidene, alkenylidene, alkylene or alkenylene group (preferably having up to 10 carbon atoms), which may carry one or more functional groups as defined above.

As indicated above, the diester groupings of formula (I) may be separated by a wide range of groupings. Where it is desired that the polymer should break down into relatively short sections to aid biodegradation, the group R^3 which separates the diester units of formula (II) may, for example, be an alkylene or alkenylene group (e.g. containing up to 20, more preferably up to 10 carbon atoms), a cycloalkylene group (preferably having up to 10 carbon atoms), an aralkylene group (preferably having up to 20 carbon atoms and which may be bonded via the aryl and/or alkyl moieties - such aralkyl groups include, for example, two aryl groups joined by an alkylene chain) or a heterocyclic group having one or more hetero-atoms selected from O, S and N (preferably having up to 20 carbon atoms). The group R^3 may carry functional groups, e.g. as set out above for R^1 and R^2 and/or substituents such as oxo groups; the carbon chains of R^3 groups may be

interrupted and/or terminated by heteroatoms such as O, N or S, e.g. in conjunction with oxo substituents to form linkages such as ester, thioester or amide groups. In order to enhance hydrophilicity of the polymers R^3 may for example comprise one or more sets of oxyethylene or polyoxyethylene units and/or hydroxyl-substituted carbon chains (e.g. as in hydroxyalkyl groups or sugar groups). Such sets of units may, for example, be linked through oxycarbonyl groups, e.g. by short chain diacid groups such as oxalyl, malonyl, succinyl, glutaryl or adipoyl.

Where the group R^3 comprises a polymeric grouping, this may, for example, be a polyamide, poly(hydroxy acid), polyester, polycarbonate, polysaccharide, polyoxyethylene, polyoxyethylene-polyoxypropylene block copolymer, polyvinyl alcohol or polyvinyl ether/alcohol grouping.

The wide range of possible groups R^1, R^2 and R^3 enables the hydrophobicity or hydrophilicity of the polymer to be adjusted to any required use. Thus, the polymers may advantageously be designed to be water-insoluble but yield water-soluble degradation products upon enzymic hydrolysis.

Aliphatic groups present as, for example, R^1 and R^2 may be straight or branched, saturated or unsaturated and include, for example, alkyl and alkenyl groups, e.g. methyl, ethyl, propyl, isopropyl, butyl, decyl or allyl groups. Araliphatic groups include (monocarbocyclic aryl)-alkyl groups, for example benzyl groups. Aryl groups include mono- or bi-cyclic aryl groups, for example phenyl, tolyl or naphthyl groups. Heterocyclic groups include 5- or 6- membered heterocyclic groups preferably having one heteroatom, for example furyl, thienyl or pyridyl groups. Halogen atom substituents may, for example, be chlorine, bromine or iodine.

Biodegradation of polymers containing units of formula (III) will in general take place by enzymic hydrolytic cleavage of the bonds linking the group $-O-C(R^1R^2)-O-$ to the adjacent carbonyl groups, generally yielding an aldehyde or ketone of the formula R^1-CO-R^2.

The intervening sections will form different products according to whether m or n is zero or 1. Where m or n is zero, hydrolytic cleavage will generally yield a carboxyl group; where m or n is 1, a hypothetical carbonic acid group $-R^3-O-COOH$ is formed which generally eliminates carbon dioxide to form a grouping $-R^3-OH$. This can be of use where liberation of carbon dioxide is physiologically or functionally desirable.

As indicated above, the units of formula (III) may be different within the same polymer, i.e. the polymers may be copolymers such as block or graft copolymers. The polymers may be copolymers formed with non-biodegradable monomers; the non-biodegradable sections remaining after enzymic or other cleavage are preferably of acceptable size to ensure their water-solubility or water-dispersibility and thus permit ready dispersal or removal; it is possible to consider such non-biodegradable sections as part of the groupings R^3 in formula (III) which, in effect, link together the biodegradable groupings of formula (II).

The polymers may be linear, branched or crosslinked. Branched and crosslinked polymers will in general make use of functional groups or double bonds in the corresponding R^1, R^2 or R^3 groups of their monomers. The resulting crosslinked or branched polymers will thus contain some units of formula (III) wherein R^1, R^2 and/or R^3 are substituted with the crosslinking or branched chains.

In general, where the carbon atoms linking the groups R^3 to the groupings of formula (II) are chiral, the chirality is preferably that found in natural products since the degrading enzymes will generally act more efficiently on such structures.

It has been generally observed that in crosslinked biodegradable polymers the crosslinking sections are often degraded first, thus exposing the rest of the network to enzymic hydrolysis. It is particularly useful, therefore, to have groups of formula (II) in the crosslinking chains of a polymer. One possibility is thus to convert a water-

soluble long chain natural or synthetic non-biodegradable or slowly biodegradable substance, e.g. a polysaccharide or oligosaccharide, or a short chain polyacrylamide, into a water-insoluble form by crosslinking using crosslinking units containing groupings of formula (II). This may minimise the cost of the final product by reducing the amount of the relatively expensive biodegradable units of formula (II).

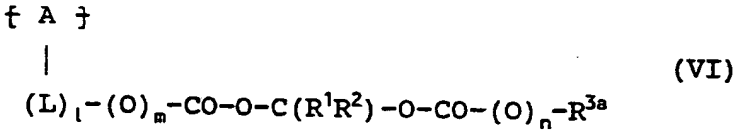
Block copolymers may, for example, have the structure

$$\text{-}\{(O)_n\text{-}CO\text{-}O\text{-}C(R^1R^2)\text{-}O\text{-}CO\text{-}(O)_m\text{-}R^3\}_q^A\text{-}\{(O)_n\text{-}CO\text{-}O\text{-}C(R^1R^2)\text{-}O\text{-}CO\text{-}(O)_m\text{-}R^3\}_r^B\text{-}$$

where the respective values of R^1, R^2, R^3, m and n are such that the repeating units in blocks A and B are different and q and r are integers, e.g. 10-20. One or more further blocks may be attached to those shown above.

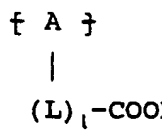
Polymers containing units of formula (III) which are useful in accordance with the present invention may, for example, be prepared as described in the aforementioned Application No. WO 92/04392.

Another class of polymers useful in accordance with the invention contain units of formula (VI)



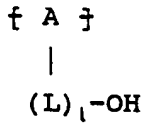
(VI)

where A represents a repeating unit of a non-polypeptide polymer backbone chain; L represents a linking group; l is zero or 1; m, n, R^1 and R^2 are as hereinbefore defined; and R^{3a} represents a lipophilic organic group, e.g. an organic group as hereinbefore defined for R^1 and R^2. The group A and the group L (where present) should be such that the polymeric degradation products resulting from biodegradative cleavage of the methylene diester grouping, which typically contains units of formula (VII)



(VII)

(where A, L and 1 are as hereinbefore defined) when m in formula (VI) is zero and units of formula (VIII)



(VIII)

(where A, L and 1 are as hereinbefore defined) when m in formula (VI) is 1, are water-soluble.

Factors influencing the water solubility of these polymeric degradation products include the nature of the repeating units A and any comonomer units which may be present, the length of any linking group L, and the overall chain length of the polymer.

Repeating units A and any comonomer units are preferably comparatively short, for example containing up to 10, e.g. 1-6 carbon atoms and may optionally be interrupted by one or more heteroatoms selected from oxygen, nitrogen and sulphur and/or substituted by one or more substituents comprising such heteroatoms (e.g. as in oxo, hydroxy and amino groups). Where hydrophilic groups are included in the repeating units A and/or any comonomer units, the size of these units need not be limited and possible units thus include polyoxyethylene (e.g. as in polyoxyethylene esters of methacrylic acid).

Any linking groups L are preferably of short length and include, for example, C_{1-3} alkylene groups such as methylene, ethylene or propylene optionally linked to the polymer backbone by and/or (where appropriate) interrupted by, for example, oxy, carbonyl, oxycarbonyl, imino or iminocarbonyl groups. Where polar groupings such as oxygen atoms or imino groups are present the linking groups may be longer without unduly inhibiting water solubility. Suitable polymeric degradation products thus

include, for example, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, polyhydroxyalkyl acrylates and methacrylates such as poly(2-hydroxyethyl acrylate), polysaccharides such as starch and dextran, polyesters, polyethers such as polyoxyethylenes and polyoxypropylenes, polyacrylamides and polymethacrylamides such as poly(N-hydroxyalkyl) acrylamides and methacrylamides (e.g. poly N-(2-hydroxypropyl)methacrylamide), polyamides, polyurethanes and epoxy polymers.

In general the polymeric degradation products of biodegradable polymers containing units of formula (VI), by virtue of their water solubility, need not themselves be biodegradable; they may thus, for example, be polyvinylic or polyacrylic. The invention therefore includes the use of polymers containing units of formula (VI) in which A is a repeating unit of a polyolefin, for example ethylene or propylene. It will be appreciated that polymers of this type may be prepared by free radical polymerisation techniques with comparative ease and economy, in contrast with, for example, the more complex polypeptide synthesis techniques needed to prepare polymers such as those described in EP-A-0130935.

The nature and size of R^1, R^2 and R^{3a} in units of formula (VI) will influence both the level to which polymers containing such units are rendered lipophilic and thus insolubilised with respect to water and the rate at which the side chain is biodegradably cleaved. Thus large and/or bulky groups will tend to reduce the rate of biodegradation through steric hindrance, while increasing the lipophilicity of the polymer. In one useful category of side chain R^1 and R^2 are each selected from hydrogen atoms and C_{1-4} alkyl groups such as methyl, and R^{3a} represents a lower alkyl group, e.g. containing at least 3 carbon atoms as in propyl and butyl groups; such side chains combine substantial degrees of lipophilicity and biodegradability.

It will be appreciated that e.g. linear polymers containing units of formula (VI) may exhibit enhanced

processability parameters (e.g. solubility in organic solvents and melt processability) compared to crosslinked polymers, e.g. containing crosslinking groups incorporating units of formula (II). In this respect they may also be contrasted with the polymers described in EP-A-0130935, which have the potential disadvantage that the high level of hydrogen bonding exhibited by polypeptides will tend to cause them to have relatively high melting points, such that they may not be melt processable without undue degradation occuring.

Polymers containing units of formula (VI) may be prepared in any convenient way, for example by either (A) reaction of a preformed water-soluble polymer with a reagent serving to introduce the desired lipophilic methylene diester side chain, or (B) polymerisation of a functional monomer which carries the desired lipophilic methylene diester side chain.

Process (A) may be effected by, for example, reaction of a polymer having pendant alcoholic hydroxyl groups (e.g. polyvinyl alcohol, a polyhydroxyalkyl acrylate or methacrylate or a polysaccharide) with a compound of formula (IX)

$$X\text{-}CO\text{-}O\text{-}C(R^1R^2)\text{-}O\text{-}CO\text{-}(O)_n\text{-}R^{3a} \qquad (IX)$$

(where R^1, R^2, R^{3a} and n are as hereinbefore defined and X represents a leaving group such as a halogen atom, e.g. fluorine, chlorine, bromine or iodine). Reagents of formula (IX) may, for example, be prepared as described by Folkmann and Lund, Synthesis 1990, 1159. Such reactions, which will yield polymers containing units of formula (VI) in which m is 1, are conveniently effected in solution, for example in a solvent such as tetrahydrofuran, in the presence of a weakly nucleophilic base such as pyridine. A catalytic amount of a tertiary amine such as 4-dimethylaminopyridine may also be employed. The number of polymer hydroxyl groups which are reacted to form the desired lipophilic methylene diester

groups may be controlled by appropriate choice of factors such as reagent quantities and reaction time and temperatures to affect the final hydrophilic-lipophilic balance of the lipophilised polymer. The product may be purified by standard techniques such as solvent extraction and/or dissolution/reprecipitation and/or flash chromatography.

Alternatively, process (A) may be effected by reaction of a polymer having pendant carboxyl groups (e.g. polyacrylic acid, polymethacrylic acid or a water-soluble peptide) with a compound of formula (X)

$$X\text{-}CR^1R^2\text{-}O\text{-}CO\text{-}(O)_n\text{-}R^{3a} \qquad (X)$$

(where R^1,R^2,R^{3a}, X and n are as hereinbefore defined). Such reactions, which will yield polymers containing units of formula (VI) in which m is zero, are conveniently effected in solution, for example in a solvent such as N,N-dimethylformamide, in the presence of a strong base, for example an alkali metal alkoxide such as potassium t-butoxide. A catalytic amount of a crown ether such as 18-crown-6 may also be employed. Again the hydrophilic-lipophilic balance of the polymer product can be controlled by appropriate selection of reaction parameters to determine the number of carboxyl groups which are reacted, and the product may be purified by conventional techniques.

Reagents of formula (X) may be prepared by, for example, reaction of an aldehyde or ketone of formula R^1-CO-R^2 with an acid halide or haloformate ester of formula R^{3a}-$(O)_n$-CO-X, e.g. in the presence of a catalyst such as zinc chloride or pyridine.

Process (A) may also be effected by, for example, reaction of a polymer carrying functional groups such as epoxy groups with a reagent containing the desired lipophilic methylene diester grouping and having a terminal grouping reactive with such functional groups; terminal groups reactive with epoxy groups include amino,

hydroxyl and carboxy groups. Similarly, the latter groups may be present in the initial polymer and the reagent may carry a terminal epoxy group.

Where the products are for intravenous use it is generally preferred that polymer starting materials employed in process (A) have a molecular weight of not more than about 40,000. Where the products are for other applications the molecular weight need not be critical.

Process (B) may be effected using any monomers which can be polymerised or copolymerised to form non-crosslinked polymers and which possess one or more substituents which do not participate in the polymerisation and which may be derivatised prior to polymerisation to introduce the desired lipophilic methylene diester grouping. Free radical, condensation and ionic polymerisation techniques may be employed.

Free radical polymerisation may, for example, be effected using carboxy group-containing monomers such as acrylic acid or methacrylic acid derivatised by reaction with a compound of formula (X) or by using hydroxyl group-containing monomers such as 2-hydroxyethyl acrylate or N-(2-hydroxypropyl)methacrylamide derivatised by reaction with a compound of formula (IX). Alternatively hydroxyl group-containing monomers may be reacted with a compound of formula (XI)

$$X\text{-}CO\text{-}O\text{-}C(R^1R^2)\text{-}X \qquad (XI)$$

(where R^1,R^2 and X are as hereinbefore defined) and the resulting product reacted with an appropriate salt of a carboxylic acid R^{3a}-COOH.

Free radical polymerisation may also be effected using vinyl carbonate esters of formula (XII)

$$CH_2=CH\text{-}O\text{-}CO\text{-}O\text{-}C(R^1R^2)\text{-}O\text{-}CO\text{-}(O)_n\text{-}R^{3a} \qquad (XII)$$

(where n, R^1, R^2 and R^{3a} are as defined above). Such monomers, for example having n=0, may be prepared by reaction of vinyl chloroformate with an aldehyde or ketone

$R^1R^2C=O$ in the presence of a catalytic amount of, for example, pyridine or a Lewis acid, to give an optionally substituted chloromethyl vinyl carbonate of formula (XIII)

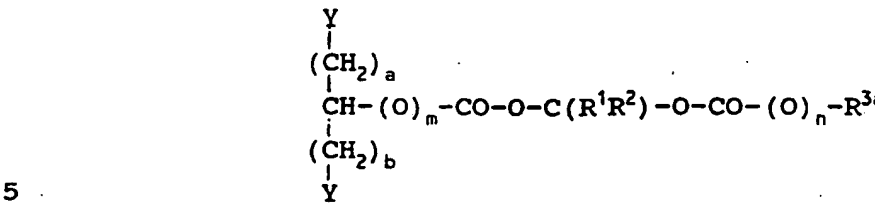
$$CH_2=CH-O-CO-O-C(R^1R^2)-Cl \qquad (XIII)$$

(where R^1 and R^2 are as defined above), followed by reaction with e.g. an appropriate salt of a carboxylic acid R^{3a}-COOH, preferably in the presence of a catalytic amount of a suitable crown ether. It will be appreciated that compounds (XII) may formally be regarded as "vinyl alcohol" derivatised by a compound of formula (IX). Polymers derived therefrom should accordingly be enzymatically biodegradable to polyvinyl alcohol.

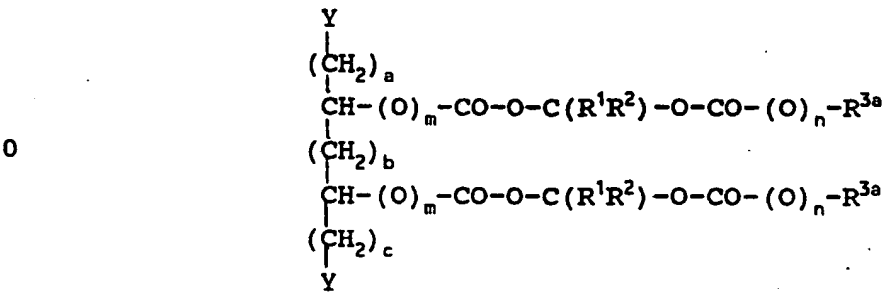
Conventional bulk, solution, emulsion and suspension polymerisation techniques may be employed. The molecular weight of the polymer product, which for intravenous use preferably should not exceed about 40,000, may be controlled by the use of chain transfer agents such as mercaptans, from which the growing polymer chain can abstract a proton leading to chain termination and formation of a sulphur radical which will initiate a new polymer chain; the molecular weight of the polymer will thus be governed by the type and concentration of the transfer agent.

Appropriate vinyl monomers, e.g. having a carbonyl group adjacent to the vinyl group, as in acrylic or methacrylic esters, for example prepared as described above, may also be subjected to ionic polymerisation techniques, both anionic and cationic; such techniques are particularly suited to the production of well-defined molecular weight polymer, especially comparatively low molecular weight materials.

Condensation polymerisation may be effected using a wide range of appropriately functionalised monomers, examples of which may be represented by formulae (XIV) and (XV)



(XIV)



(XV)

(where R^1,R^2,R^{3a}, m and n are as hereinbefore defined, Y is a reactive grouping such as carboxy, hydroxyl or an epoxy group such as 2,3-epoxypropyloxy, and a, b and c may each be zero or a small integer such as 1,2 or 3). In formula (XV) the groups R^1, R^2 and R^3 and m and n may be the same or different in the two side chains. Such monomers may be employed in conventional condensation reactions with, as appropriate, reagents such as dicarboxylic acids, dialcohols, diamines, di(acid chlorides), diisocyanates and bisepoxy compounds to yield polymers such as polyesters, polyamides, polyurethanes and epoxy polymers. The molecular weight of the polymer product may be controlled by selection of appropriate reaction times, temperatures etc and/or by use of monofunctional chain terminators.

Where appropriate, the polymers may be prepared using emulsion polymerisation techniques; this may be of particular value where, for example, it is desired to prepare the polymers in the form of monodisperse particles. Methods of emulsion polymerisation to produce particles, especially monodisperse particles, are described in EP-A-0003905, EP-A-0091453, EP-A-0010986 and EP-A-0106873.

Polymers used in contrast agents according to the

invention may advantageously be of relatively low molecular weight, e.g. not exceeding 40,000, since this may aid both biodegradation and dispersal of the degradation products. Accordingly the term "polymer" as used herein in relation to the invention should be understood to include low molecular weight materials such as oligomers.

It will be appreciated that since the polymers are to be used for medical purposes they must form non-toxic, physiologically acceptable degradation products; the groups R^1,R^2,R^3 and R^{3a} in units of formulae (III) and (VI) should therefore be selected with this requirement and the need for the degradation products to be readily dispersible in mind. Carbon dioxide liberated by cleavage of carbonate ester groupings will normally be physiologically acceptable.

The contrast agents of the invention may be used in a variety of diagnostic imaging techniques, including ultrasound, MR and X-ray imaging. Their use in diagnostic ultrasonic imaging and in MR imaging, e.g. as susceptibility contrast agents, constitute preferred features of the invention.

Any biocompatible gas may be employed in the contrast agents of the invention, for example air, nitrogen, oxygen, hydrogen, nitrous oxide, carbon dioxide, helium, argon, sulphur hexafluoride and low molecular weight optionally fluorinated hydrocarbons such as methane, acetylene or carbon tetrafluoride. The gas may be free within the microbubble or may be trapped or entrained within a containing substance. The term "gas" as used herein includes any substances in gaseous form at 37°C.

Gas precursors include carbonates and bicarbonates, e.g. sodium or ammonium bicarbonate and aminomalonate esters.

For ultrasonic applications such as echocardiography, in order to permit free passage through the pulmonary system and to achieve resonance with the preferred imaging

frequency of about 0.1-15 MHz, it may be convenient to employ microbubbles having an average size of 0.1-10 μm, e.g. 1-7 μm. Substantially larger bubbles, e.g. with average sizes of up to 500 μm, may however be useful in other applications, for example gastrointestinal imaging or investigations of the uterus or Fallopian tubes.

If desired the microbubbles may incorporate particulate stabilisers, for example amphiphiles and inorganic materials such as silica or iron oxide which are only partially wetted by the solvent system employed, e.g. having a particle size of 1-500 nm. Colloidal silica having a particle size of 5-50 nm may advantageously be employed for this purpose.

The contrast agents of the invention may be prepared in a number of ways, generally by emulsion techniques which are known in the polymer art. Thus, for example, microencapsulation techniques for the preparation of microcapsules having a wall or membrane of polymeric material are described in literature such as "Microencapsulation and Related Drug Processes" by P.D. Deasy, Marcel Dekker Inc., New York (1984).

One useful method corresponds to the interfacial deposition technique described in the above-mentioned EP-A-0458745 and comprises dissolving or suspending the polymeric wall-forming material in a water-immiscible low boiling organic solvent (for example an aliphatic or cycloaliphatic hydrocarbon or perfluorocarbon, e.g. containing up to 10 carbon atoms, or an appropriate ether, ester or other lipophilic solvent), emulsifying (e.g. by high shear mixing) the resulting solution or suspension in an aqueous phase (preferably containing a surfactant to stabilise the resulting oil in water emulsion), and subsequently removing the organic phase (e.g. by evaporation or lyophilisation, preferably under an atmosphere of the gas which is desired to be incorporated) whereby the polymer forms a membrane at the interface between the aqueous and organic phases.

The size of the microparticles/microballoons so

formed can be controlled by adjusting the stirring speed during emulsification, faster stirring tending to yield smaller particles, and is also affected by the nature of the surfactant which may, for example, be selected from fatty acids (e.g. straight chain saturated or unsaturated acids containing 10-20 carbon atoms) and carbohydrate and triglyceride esters thereof, phospholipids (e.g. lecithin), proteins (e.g. human serum albumin), polyoxyethylenes and block copolymers consisting of hydrophilic and hydrophobic blocks (e.g. polyoxyethylene - polyoxypropylene block copolymers such as Pluronics). Such emulsifiers are typically used in amounts of 1-10% w/v relative to the aqueous phase. Conventional additives may also be incorporated into the polymer; thus, for example, materials such as polyethylene glycols may be introduced to modify the flexibility and/or polarity of the membrane. Alternatively the polymer particles may be coated with, for example, polyethylene glycol units, proteins or polysaccharides to modify their aggregation tendencies and/or biological properties.

The porosity of the membrane, and therefore its permeability to solvents, solutes and gases, may also be controlled, being dependent on the difference in boiling point between the volatile organic phase and the surrounding aqueous phase; thus the porosity of the membrane increases with increasing difference between the said boiling points.

Alternatively the polymer may be dissolved in an appropriate organic solvent (e.g. methylene dichloride, dimethyl sulphoxide, tetrahydrofuran or dimethylformamide) and then dispersed (e.g. using a high speed stirrer) in an aqueous phase (preferably containing a polymeric material such as polyvinyl alcohol or a poloxamer) so as to precipitate particulate polymeric material which may be collected and lyophilised to yield porous microparticulate polymer in accordance with the invention. Such techniques are described in the above-mentioned EP-A-0458079.

Variants for the preparation of microparticles include injecting the organic polymer solution, preferably together with a physiologically acceptable stabiliser such as hydroxypropyl cellulose, into liquid nitrogen. Alternatively the polymer may be dissolved in an appropriate organic solvent (e.g. methylene chloride or tetrahydrofuran), followed by spray drying of the solution, or of an oil in water or water in oil emulsion of the organic polymer solution with an aqueous phase.

Microparticles in accordance with the invention may also be prepared using coacervation or double emulsion techniques, e.g. as described in the above-mentioned WO 91/12823. Thus, for example, an aqueous phase containing a water-soluble polymer (hereafter referred to as the "prepolymer") may be emulsified with a volatile organic solvent (e.g. an aliphatic or cycloaliphatic hydrocarbon or perfluorocarbon containing up to 10 carbon atoms) to form an oil in water emulsion. Addition of a coacervating agent (e.g. a dehydrating agent such as isopropanol or a salt such as sodium sulphate) induces concentration of the "prepolymer" around the oil droplets, whereupon a surfactant is desirably added to inhibit agglomeration of the microparticles, which are formed by crosslinking the prepolymer to introduce biodegradable units of formula (II), thereby generating water-insoluble porous polymer microparticles which may be dried by lyophilisation. Appropriate crosslinking techniques and reagents for crosslinking water-soluble "prepolymers" such as polyacrylamides are described in detail in our aforementioned International Application No. WO 92/04392.

The contrast agents of the invention may be stored and transported in dry form, in which condition they will normally be stable indefinitely, being mixed with an appropriate liquid carrier (e.g. sterile water for injection, physiological saline or phosphate buffer) prior to administration. In this way the concentration of the injected or otherwise administered contrast agent may be

varied at will, depending on the precise nature of the application. They may also be stored in suspension in such carriers, especially, in the case of microballoons, when the porosity of the encapsulating polymer membrane is comparatively low, being substantially completely stable in aqueous media in the absence of esterase enzymes.

The following non-limitative Examples serve to illustrate the invention.

GENERAL

Methacrylic acid was distilled under high vacuum to remove the stabiliser.

2,2'Azobisisobutyronitrile (AIBN) thermal initiator was purified by recrystallisation from methanol.

All reactions were carried out under N_2.

Size Exclusion Chromatography (SEC):

Pump: Knauer HPLC pump 64

Detector: Knauer Differential refractometer

Columns: Polymer Laboratories PL gels columns in series Pore sizes 10^4Å, 500Å, and 100Å, particle size 5μm, length 30, 30 and 60 cm respectively.

Solvent: THF

Calibration: Polystyrene standards (Polymer Laboratories)

Flow rate marker: Toluene

Software: Polymer Laboratories GPC/SEC software version 5.10

Mw: weight average molecule weight

Mn: number average molecule weight

Mw/Mn: polydispersity

Mp: molecular weight at maximum detector height

List of abbreviations

Tg:	glass transition temperature
TBA-OH:	tetrabutylammonium hydroxide
TBA:	tetrabutylammonium
AIBN:	2,2'-azobisisobutyronitrile
SO_2Cl_2:	sulfuryl chloride
EtSCl:	ethanesulfenyl chloride
DBU:	1,8-diazabicyclo[5.4.0]undec-7-ene(1,5-5)
$MgSO_4$:	magnesium sulphate
THF:	tetrahydrofuran
DMF:	N,N-dimethylformamide
HSA:	human serum albumin

EXAMPLE 1 - Preparation of intermediates

a) Methylene dimethacrylate

A solution of potassium hydroxide (1.00 M, 40.00 ml) was added to methacrylic acid (3.44 g, 40.00 mmol) at 0°C and the solution freeze dried for 16 hours. Dry dimethylformamide (230 ml) was added and the suspension heated to 60°C under a dry nitrogen atmosphere. Diiodomethane (1.61 ml, 20.00 mmol) was added in two portions during 10 min. and the reaction mixture left for 4 days at 60°C. The solvent was removed under reduced pressure (0.05 mmHg), before diethyl ether (140 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and water (50 ml) were added. The aqueous layer was extracted with diethyl ether (6 x 60 ml) and the combined ether-extracts washed with water (4 x 50 ml), dried ($MgSO_4$), and evaporated to give 2.63 g (72%) of the title compound.
^1H NMR (60 MHz, $CDCl_3$): δ 1.97 (2 x CH_3, m), 5.63 (2 x H-C=, m), 5.88 (CH_2, s), 6.18 (2 x H-C=, m).
IR (film, cm^{-1}): 2987 (w), 2962 (w), 2930 (w), 1732 (str), 1638 (w), 1454 (w), 1315 (w), 1295 (w), 1158 (w), 1100 (str), 1012 (m), 989 (m).

b) Methylene bis(16-hydroxyhexadecanoate)

(i) 16-Triphenylmethoxyhexadecanoic acid

A solution of 16-hydroxyhexadecanoic acid (1.36 g, 5.00 mmol), triphenylmethyl chloride (1.53 g, 5.50 mmol), triethylamine (1.25 ml) and 4-dimethylaminopyridine (10.03 g, 0.25 mmol) was stirred overnight in dry dimethylformamide at ambient temperature under nitrogen. After 16 hours stirring, the brown cloudy solution was poured into ice-water and extracted with dichloromethane (5 x 50 ml). The organic phases were washed with saturated ammonium chloride solution (2 x 100 ml), water (2 x 100 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product purified by flash chromatography on a silica column with dichloromethane/methanol (20:1) as eluent to yield the title compound as a yellow oil (0.41 g).

^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 25.7, 26.3, 29.2, 29.5, 29.6, 29.7, 30 32.8, 34.1, 62.9, 63.7, 86.2, 144.5, 177.2.

MS (CI): 515 (M + H)

(ii) 16-Triphenylmethoxyhexadecanoic acid cesium salt

Aqueous cesium carbonate (1M, 0.16 ml) was added dropwise to a solution of 16-triphenylmethoxyhexadecanoic acid (0.16 g, 0.31 mmol) from Example 1b(i) above in tetrahydrofuran (10 ml) until the pH reached approximately 8, whereupon the solvent was removed under reduced pressure and the residue dried under vacuum for 2 hours. The oily semicrystalline residue was dispersed in dry dimethylformamide (10 ml) and evaporated to dryness in vacuo.

(iii) Methylene bis(16-triphenylmethoxyhexadecanoate)

Diiodomethane (0.04 g, 0.16 mmol) was added to a suspension of 16-triphenylmethoxyhexadecanoic acid cesium salt (0.31 mmol) from Example 1b(ii) above in dry dimethylformamide (10 ml). The reaction mixture was heated

at 60°C for 2 days under nitrogen. The solvent was removed in vacuo, and the product purified by flash chromatography on a 2 x 5 cm silica column with chloroform as eluent to yield the title compound as a brown oil (0.10 g).

^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 26.3, 29.0, 29.2, 29.4, 29.5, 29.6, 29.7, 30.0, 34.0, 63.7, 79.0, 86.2, 126.7, 127.2, 127.6, 127.9, 128.7, 144.5, 172.5.

(iv) Methylene bis(16-hydroxyhexadecanoate)

Methylene bis(16-triphenylmethoxyhexadecanoate) (0.07g, 0.07 mmol) from Example 1b(iii) above was dissolved in glacial acetic acid (8 ml) and heated at 55°C. The reaction was monitored by TLC. After 10 hours the reaction mixture was poured onto ice, and the crude product was filtered, washed with aqueous sodium bicarbonate and water, and dried under reduced pressure. The product was purified by flash chromatography on a silica column with chloroform/ methanol (20:1) as eluent to yield the title compound as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2-1.4 (m, 44H), 1.5-1.6 (m, 8H) 2.35 (t, 4H), 3.64 (t, 4H), 5.75 (s, 2H).

c) Methylene bis(12-hydroxydodecanoate)

DBU (2.0 mmol) was added to a solution of 12-hydroxydodecanoic acid (2.0 mmol) in DMF (2 ml). The solution was stirred for 5 min before CH_2I_2 (1.0 mmol) was added, and the solution was stirred for 12 hours at 60 °C. DMF was then removed under reduced pressure, and the residual material dissolved in $CHCl_3$ (50 ml), washed (10% K_2CO_3; 3 x 20 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using $CHCl_3$/MeOH 95:5 for elution; yield 75%.

^{1}H NMR ($CDCl_3$): δ 1.20-1.40 (m, 28H), 1.50-1.68 (m, 10H), 2.35 (t, J 7.5 Hz, 4H), 3.63 (t, J 6.6 Hz, 4H), 5.74 (s, 2H).

^{13}C NMR ($CDCl_3$): δ 24.62, 25.75, 28.98, 29.19, 29.40, 29.42,

29.48, 29.56, 32.80, 33.99, 63.01, 79.06, 172.53.
MS (EI): 445 (M+1, 100)

d) Methylene bis(10-hydroxydecanoate).

DBU (4.24 g, 0.027 mol) was added to 10-hydroxydecanoic acid (5.0 g, 0.027 mol) in DMF (100 ml). After 5 min. with stirring, diiodomethane (4.09 g, 0.014 mol) was added and the mixture was left stirring at room temperature for 3 days. DMF was evaporated under reduced pressure and the residue dissolved by adding chloroform (100 ml) and water (50 ml). After separating the phases the aqueous layer was extracted with chloroform (3x75 ml) and the combined organic phase was dried ($MgSO_4$). The solvent was removed under reduced pressure and flash chromatography gave 2.98 g (54.9 %) of the title product.
^{1}H NMR (60 MHz, $CDCl_3$): δ 1.30-1.80 (m, 28H, CH_2), 2.35 (m, 4H, CH_2CO), 3.65 (m, 6H, 2 X CH_2O + 2 X OH), 5.75 (s, 2H, -OCH_2O-).

e) Bis(chlorocarbonyloxymethyl) terephthalate.

(i) Bis (ethylthiocarbonyloxymethyl) terephthalate

Potassium tert. butoxide (3.24 g, 0.029 mol) was added to a solution of terephtalic acid (2.40 g, 0.014 mol) in DMF (100 ml). O-Chloromethyl S-ethyl carbonothioate[1] (4.50 g, 0.028 mol) was added to the resulting suspension. 18-crown-6 (0.23 g, 0.87 mmol) was then added and the reaction mixture was left with stirring at room temperature for 4 days. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica /chloroform) to give 3.38 g (62%) of the title product.
^{1}H NMR (60 MHz, $CDCl_3$): δ 1.30 (t, 6H, CH_3CH_2), 2.95 (q, 4H, CH_3CH_2), 5.80 (s, 4H, OCH_2O), 8.20 (s, 4H, Ph).

(ii) Bis(chlorocarbonyloxymethyl) terephthalate.

SO_2Cl_2 (0.73 g, 0.0054 mol) was added to bis(ethylthiocarbonyloxymethyl) terephthalate (1.02 g, 0.0054 mol) from Example 1e(i) above at 0-5 °C with stirring during 15 min. followed by stirring at room temperature for 45 min. Evaporation of EtSCl at room temperature and 0.1 mmHg gave light yellow crystals. Yield: 0.80 g (90%)

^{1}H NMR (60 MHz, $CDCl_3$): δ 5.76 (s, 4H, OCH_2O), 8.20 (s, 4H, Ph).

f) Methylene bis(4-hydroxymethylbenzoate)

DBU (9.90 g, 0.065 mol) was added to 4-hydroxymethyl-benzoic acid (9.89 g, 0.065 mol) in DMF (325 ml). After 5 min. with stirring, diiodomethane (8.705 g, 0.035 mol) was added and the mixture was left with stirring at room temperature for 3 days. DMF was evaporated under reduced pressure and the residue dissolved by adding chloroform (100 ml) and water (50 ml). After separating the phases the aqueous layer was extracted with chloroform (3x75 ml) and the combined organic phase was dried ($MgSO_4$). The solvent was removed under reduced pressure to give 3.0 g (27 %) of the title product.

^{1}H NMR (60 MHz, $CDCl_3$): δ 4.7 (s, 4H, HO-CH_2-Ph), 6.2 (s, 2H, O-CH_2-O), 7.4-8.2 (m, 8H, Ph).

g)-k) General procedure for chloromethyl carbonates.

To a solution of chloromethyl chloroformate and the stated alcohol in methylene chloride (200 ml), pyridine was added at 0°C. After 20 min at 0°C and 21 hours at 25°C the reaction mixture was washed with aqueous hydrochloric acid (1 M, 10 ml), aqueous saturated sodium hydrogen carbonate (10 ml) and water (10 ml). The solvent was removed under reduced pressure after drying ($MgSO_4$), giving crude chloromethyl carbonate.

Table 1

Example 1	Chloromethyl-chloroformate g , mmol	Alcohol , ROH R, (g, mmol)	Pyridine g , mmol
g	25.01, 194	CH_3, (5.64, 176)	15.52, 194
h	15.81, 124	CH_3CH_2, (5.20, 113)	9.91, 124
i	14.20, 111	$CH_3(CH_2)_5$, (8.10,109)	8.90, 113
j	20.01, 155	$CH_3(CH_2)_9$, (22.25, 139)	12.54, 157
k	20.02, 155	$PhCH_2$, (15.23, 141)	12.54, 157

g) Methyl chloromethyl carbonate.

The compound was obtained from chloromethyl chloroformate and methanol.

^1H NMR (60 MHz, $CDCl_3$) : δ 3.98 (s, 3H, OCH_3), 5.85 (s, 2H, CH_2Cl).

h) Ethyl chloromethyl carbonate.

The compound was obtained from chloromethyl chloroformate and ethanol.

^1H NMR (60 MHz, $CDCl_3$) : δ 1.25 (t, 3H, CH_3), 4.25 (q, 2H, CH_2), 5.70 (s, 2H, OCH_2Cl).

i) Butyl chloromethyl carbonate

The compound was obtained from chloromethyl chloroformate and butanol.

^{1}H NMR (60 MHz, $CDCl_3$) : δ 0.86 (m, 3H, CH_3CH_2), 1.40 (m, 4H, CH_2CH_2), 4.15 (t, 2H, CH_2-O), 5.63 (s, 2H, OCH_2Cl).

j) Decyl chloromethyl carbonate.

The compound was obtained from chloromethyl chloroformate and decyl alcohol.

^{1}H NMR (60 MHz, $CDCl_3$): δ 0.90-1.50 (m, 19H, CH_3 and CH_2), 4.20 (m ,2H, CH_2O), 5.75 (s, 2H, OCH_2Cl).

k) Benzyl chloromethyl carbonate.

The compound was obtained from chloromethyl chloroformate and benzyl alcohol.

^{1}H NMR (60 MHz, $CDCl_3$) : δ 5.20 (s, 2H, $PhCH_2O$), 5.70 (s, 2H, $ClCH_2O$), 7.32 (s, 5H, Ph).

l)-p) General procedure for methacryloyloxymethyl carbonates.

Potassium tert. butoxide was added to a solution of methacrylic acid in DMF (200 ml). Chloromethyl carbonate from Example 1g-k above was added to the resulting suspension. 18-crown-6 was then added and the reaction mixture was left with stirring at room temperature for 24 hours.The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (30 ml) and washed with saturated aqueous sodium hydrogen carbonate (10 ml) and water (20 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure.

Table 2

Example	Compound from Ex. 1, (g, mmol)	Potassium methacrylate (g,mmol)	18-crown-6 (g,mmol)	DMF (ml)
l	g, (9.67, 78)	8.71, 78	1.01, 38	350
m	h, (8.04, 60)	6.73, 60	0.6, 23	300
n	i, (30.61, 122)	13.67, 122	2.5, 94	600
o	j, (30.61, 122)	13.67, 122	2.5, 94	600
p	k, (22.01, 110)	13.64, 110	1.5, 57	550

l) Methyl methacryloyloxymethyl carbonate.

The compound was obtained from methyl chloromethyl carbonate and potassium methacrylate.

IR (KBr): 1772 (C=O, str.), 1737 (C=O, str.), 1635 (C=C, str.) cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): δ 1.91 (s, 3H, $CH_3C=$), 3.79 (s, 3H, CH_3O), 5.64 (m, 1H, $CH_2=$), 5.80 (s, 2H, $-OCH_2O-$), 6.16 (m, 1H, $CH_2=$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 17.95 ($\underline{C}H_3C=$), 55.13(CH_3O), 82.18 ($-OCH_2O-$), 127.52 ($CH_2=$), 135.02 (C=), 154.44 (C=O), 165.46 (C=O).

m) Ethyl methacryloyloxymethyl carbonate.

The compound was obtained from ethyl chloromethyl carbonate and potassium methacrylate.

IR (KBr): 1772 (C=O, str), 1736 (C=O, str.), 1635 (C=C, str) cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, 3H, CH_3), 1.92 (s, 3H, $CH_3C=$), 4.23 (q, 2H,CH_2), 5.66 (m, 1H, $CH_2=$), 5.80 (s, 2H, $-OCH_2O-$), 6.20 (m, 1H, $CH_2=$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 15.70 ($\underline{C}H_3CH_2$), 19.60 ($\underline{C}H_3C=$), 65.72(CH_2O), 83.05 ($-OCH_2O-$), 127.76 ($CH_2=$), 135.40 (C=), 153.82 (C=O), 165.42 (C=O).

n) Butyl methacryloyloxymethyl carbonate.

The compound was obtained from butyl chloromethyl carbonate and potassium methacrylate.

IR (KBr): 1772 (C=O, str), 1736 (C=O, str.), 1635 (C=C, str) cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (t, 3H, $C\underline{H}_3CH_2$),1.47 (m, 2H, CH_2CH_2), 1.72 (m, 2H, CH_2CH_2), 2.01 (s, 3H, $CH_3C=$), 4.25 (t, 2H, CH_2-O), 5.74 (m, 1H, $CH_2=$), 5.89 (s, 2H, $-OCH_2O$), 6.27 (m, 1H, $CH_2=$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.47 ($\underline{C}H_3CH_2$), 17.97 ($CH_3\underline{C}H_2$), 18.71 ($\underline{C}H_3C=$), 30.36 (CH_2), 68.46 (CH_2O), 82.07 ($-OCH_2O-$), 127.46 ($CH_2=$), 135.05 (C=), 153.89 (C=O), 165.50 (C=O).

o) Decyl methacryloyloxymethyl carbonate.

The compound was obtained from decyl chloromethyl carbonate and potassium methacrylate.

IR (KBr): 1772 (C=O, str.), 1763 (C=O, str.), 1635 (C=C, str.) cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 3H, CH_3), 1.28 (m, 14H,CH_2), 1.72 (m, 2H, CH_2), 1.99 (s, 3H, $CH_3C=$), 4.21 (t, 2H, CH_2O), 5.70 (m, 1H, $CH_2=$), 5.86 (s, 3H, $-OCH_2O-$), 6.24 (m, 1H, $CH_2=$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.78 (CH_3), 17.76 ($\underline{C}H_3C=$), 22.76-31.55 (CH_2), 68.60 (CH_2O), 81.90 ($-OCH_2O-$), 127.28 ($CH_2=$), 134.86 (C=), 153.73 (C=O), 165.33 (C=O).

p) Benzyl methacryloyloxymethyl carbonate.

The compound was obtained from benzyl chloromethyl carbonate and potassium methacrylate.
IR (KBr): 3077 (Ph), 1772 (C=O, str.), 1763 (C=O, str.), 1635 (C=C, str.) cm^{-1}
^1H NMR (300 MHz, $CDCl_3$): δ 1.96 (s, 3H, $CH_3C=$), 5.22 (s, 2H, CH_2O), 5.70 (m, 1H, $CH_2=$), 5.87 (s, 3H, $-OCH_2O-$), 6.22 (m, 1H, $CH_2=$) 7.39 (s, 5H, Ph).
^{13}C NMR (75 MHz, $CDCl_3$): δ 17.96 ($\underline{C}H_3C=$), 69.91 (CH_2O), 82.03 ($-OCH_2O-$), 127.41 ($CH_2=$), 128.32 (Ph), 134.78 (C=), 153.58 (C=O), 165.28 (C=O).

q) Ethyl 1-methacryloyloxyethyl carbonate.

(i) Ethyl chloroethyl carbonate.
To a solution of chloroethyl chloroformate (23.16 g, 0.162 mol) and ethanol (7.45 g, 0.162 mol) in methylene chloride (200 ml), pyridine (12.82 g, 0.162 mol) was added at 0°C. After 10 min at 0°C and 21 hours at 25°C the reaction mixture was washed with aqueous hydrochloric acid (100 ml), aqueous saturated sodium hydrogen carbonate (100 ml) and water (100 ml). The solvent was removed under reduced pressure after drying ($MgSO_4$), giving 18.5 g (74 %) of the intermediate ethyl chloroethyl carbonate as a crude product.
^1H NMR (60 MHz, $CDCl_3$): δ 1.30 (t, 3H, CH_3), 1.85 (d, 3H, $C\underline{H}_3CH$), 4.25 (q, 2H, CH_2), 6.45 (q, 1H, CH).

(ii) Ethyl 1-methacryloyloxyethyl carbonate.
Potassium tert. butoxide (3.70 g, 0.033 mol) was added to a solution of methacrylic acid (2.84 g, 0.033 mol) in DMF (100 ml). Ethyl chloroethyl carbonate (5.08 g, 0.033 mol)

from Example 1q(i) above was added to the resulting suspension. 18-crown-6 (0.61 g, 2.3 mmol) was then added and the reaction mixture was left with stirring at room temperature for 3 days.The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (100 ml) and washed with saturated aqueous sodium hydrogen carbonate (50 ml) and water (50 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography gave 2.50 g (38 %) of the title product. (Adjusted for recovered starting material the yield was 75%).

^1H NMR (60 MHz, $CDCl_3$): δ 1.30 (t, 3H, $C\underline{H}_3CH_2$), 1.60 (d, 3H, $C\underline{H}_3CH$), 2.00 (s, 3H, $CH_3C=$), 4.20 (q, 2H, CH_2), 5.70 (m, 1H, $CH_2=$), 6.25 (q, 1H, $-OC\underline{H}(CH_3)O-$), 6.90 (m, 1H, $CH_2=$).

r) Methacryloyloxymethyl benzoate.

Potassium tert. butoxide (10.0 g, 0.090 mol) was added to a solution of methacrylic acid (7.75 g, 0.090 mol) in DMF (300 ml). Chloromethyl benzoate[2] (15.0 g, 0.088 mol) was added to the resulting suspension. 18-crown-6 (1.8 g, 6.9 mmol) was then added and the reaction mixture was left with stirring at room temperature for 2 days.The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (100 ml) and washed with saturated aqueous sodium hydrogen carbonate (50 ml) and water (50 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography gave 15.9 g (82 %) of the title product.

^1H NMR (60 MHz, $CDCl_3$): δ 2.00 (s, 3H, $CH_3C=$), 5.65 (m, 1H, $CH_2=$), 6.15 (s, 2H, $-OCH_2O-$), 6.35 (m, 1H, $CH_2=$), 7.50 (m, 3H, Ph), 8.05 (m, 2H, Ph).

s) N-(2-acetoxymethoxycarbonyloxypropyl)methacrylamide

(i) N-(2-chloromethoxycarbonyloxypropyl) methacrylamide.

To a solution of N-(2-hydroxypropyl) methacrylamide[3] (2.86 g, 20 mmol), and pyridine (1.90 g, 24 mmol) in methylene chloride (100 ml), chloromethyl chloroformate (3.87 g, 30 mmol) in methylene chloride (120 ml) was added at 0°C. After 15 min at 0°C and 24 hours at 25°C the reaction mixture was washed with water (5x25 ml). The solvent was removed under reduced pressure after drying ($MgSO_4$), Flash chromatography (silicagel, chloroform) gave 3.30 g (70 %) of the title product.

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.42 (d, 3H, $C\underline{H}_3$-CH-O), 2.0 (m, 3H, $C\underline{H}_3C$=), 3.2-4.0 (m, 2H, NH-$C\underline{H}_2$-CH), 4.8-5.3 (m, 1H, CH_3-$C\underline{H}$-O), 5.3 (m, 1H, CH_2=), 5.70 (m, 1H, CH_2=), 5.7 (s, 2H, CH_2Cl), 6.1-6.7 (br s, 1H, NH).

(ii) N-(2-acetoxymethoxycarbonyloxypropyl)methacrylamide

Method 1:

A THF solution (30 ml) of TBA acetate (1.21 g, 4 mmol) prepared by freeze-drying an aqueous solution of equimolar TBA-OH and acetic acid, was added to a stirred solution of N-(2-chloromethoxycarbonyloxypropyl)methacrylamide (0.943, 4 mmol) from Example 1s(i) above in THF (10 ml) at room temperature. Following stirring for 5 days the solvent was removed under reduced pressure. The residue was dissolved in chloroform (50 ml) and washed with water (5x10 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography (silicagel, hexane/ethyl acetate (3:4)) gave 0.486 g (47 %) of the title product.

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.4 (d, 3H, $C\underline{H}_3$-CH-O), 2.0 (s, 3H, $C\underline{H}_3C$=), 2.2 (s, 3H, CH_3C=O), 3.2-4.0 (m, 2H, NH-$C\underline{H}_2$-CH), 4.8-5.3 (m, 1H, CH_3-$C\underline{H}$-O), 5.3 (m, 1H, CH_2=), 5.70 (m, 1H, CH_2=), 5.8 (s, OCH_2O), 6.1-6.7 (br s, 1H, NH)

Method 2:

To a solution of N-(2-hydroxypropyl)-methacrylamide[3] (0.430 g, 3.0 mmol) and pyridine (0.285g, 3.6 mmol) in methylene chloride (30 ml), acetoxymethyl chloroformate (0.500 g, 3.3 mmol) in methylene chloride (6 ml) was added at 0°C. After 10 min at 0°C and 3 days at room temp. the reaction mixture was washed with water (100ml). The solvent was removed under reduced pressure after drying ($MgSO_4$). Flash chromatography (silicagel, hexane/ethyl acetate (3:4)) gave 0.40 g (51 %) of the title product.

NMR data were in good agreement with those above.

t) N-[2-(1-acetoxyethoxycarbonyloxy)propyl]methacrylamide.

(i) N-[2-(1-chloroethoxycarbonyloxy)propyl]methacrylamide.

To a solution of N-(2-hydroxypropyl)methacrylamide[3] (3.15 g, 22 mmol), and pyridine (2.088 g, 26.4 mmol) in methylene chloride (100 ml), 1-chloroethyl chloroformate (4.718 g, 33 mmol) in methylene chloride (20 ml) was added at 0°C. After 10 min at 0°C and 5.5 hours at 25°C the reaction mixture was washed with water (5x40 ml). The solvent was removed under reduced pressure after drying ($MgSO_4$) to give 4.84 g (88%) of the title product.

^1H NMR (60 MHz, $CDCl_3$): δ 1.37 (d, 3H, CH_2-CH(CH_3)O-), 1.83 (d, 3H, CH_3-CH-Cl), 1.97 (m, 3H, CH_3C=), 3.3-3.6 (m, 2H, NH-CH_2-CH), 4.7-5.3 (m, 1H, CH_2-CH(CH_3)-O), 5.3 (m, 1H, CH_2=), 5.70 (m, 1H, CH_2=), 6.0-6.6 (m, 2H, NH + -Cl-CH-CH_3).

(ii) N-[2-(1-acetoxyethoxycarbonyloxy)propyl]-methacrylamide.

A THF solution (100 ml) of TBA acetate (6.93 g, 23 mmol) prepared by freeze-drying an aqueous solution of equimolar TBA-OH and acetic acid, was added to a stirred solution of N-[2-(1-chloroethoxycarbonyloxy)propyl]methacrylamide (4.736 g, 19 mmol) from Example 1t(i) above in THF (100 ml) at room temperature. Following stirring for 4 days the solvent was removed under reduced pressure. The residue

was dissolved in chloroform (100 ml) and washed with water (5x20 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography (silicagel, hexane/ethyl acetate (3:4)) gave 1.29 g (25 %) of the title product.
^1H NMR (60 MHz, $CDCl_3$): δ 1.3 (d, 3H, CH_2-CH($C\underline{H}_3$)O-), 1.5 (d, 3H,O-CH(CH_3)O), 2.0 (m, 3H, $C\underline{H}_3C$=), 2.1 (s, 3H, CH_3C=O), 3.3-3.6 (m, 2H, NH-$C\underline{H}_2$-CH), 4.7-5.3 (m, 1H, CH_2-$C\underline{H}$(CH_3)-O), 5.4 (m, 1H, CH_2=), 5.7 (m, 1H, CH_2=), 6.1-6.6 (br s, 1H, NH), 6.6-6.9 (m, 1H, O-$C\underline{H}$(CH_3)O)

u) Methyl 1-methacryloyloxyethyl carbonate.

(i) Methyl 1-chloroethyl carbonate.

To a solution of 1-chloroethyl chloroformate (35.74 g, 0.25 mol) and methanol (8.00 g, 0.25 mol) in methylene chloride (300 ml), pyridine (19.78 g, 0.25 mol) was added at 0°C. After 10 min at 0°C and 2 days at 25°C the reaction mixture was washed with aqueous hydrochloric acid (100 ml), aqueous saturated sodium hydrogen carbonate (100 ml) and water (100 ml). The solvent was removed under reduced pressure after drying ($MgSO_4$), giving 25.5 g (74 %) of the intermediate methyl 1-chloroethyl carbonate as a crude product.
^1H NMR (60 MHz, $CDCl_3$): δ 1.85 (d, 3H, $C\underline{H}_3CH$), 3.80 (s,3H, CH_3O), 6.50 (q, 1H, CH).

(ii) Methyl 1-methacryloyloxyethyl carbonate.

Potassium tert. butoxide (3.70 g, 0.033 mol) was added to a solution of methacrylic acid (2.84 g, 0.033 mol) in DMF (100 ml). Methyl 1-chloroethyl carbonate (4.55 g, 0.033 mol) from Example 1u(i) above was added to the resulting suspension. 18-crown-6 (0.61 g, 2.3 mmol) was then added and the reaction mixture was left with stirring at room temperature for 3 days.The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (100 ml) and washed

with saturated aqueous sodium hydrogen carbonate (50 ml) and water (50 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography gave 4.46 g (72 %) of the title product.
^{1}H NMR (60 MHz, $CDCl_3$): δ 1.65 (d, 3H, $C\underline{H}_3CH$), 2.00 (s, 3H, CH_3C=), 3.90 (s, 3H, CH_3O), 5.65 (m, 1H, CH_2=), 6.25 (m, 1H, CH_2=), 6.90 (q, 1H, $C\underline{H}CH_3$).

v) Ethylene di(chloromethyl carbonate).

Chloromethyl chloroformate (19.12 g, 148.5 mmol) was added to an ice-cooled (0°C) solution of ethylene glycol (2.8 ml, 50 mmol) in CH_2Cl_2(200 ml). Pyridine (8.70 g, 110 mmol) was then added and the reaction mixture was left with stirring for 15 min. at 0°C and 6 hours at room temperature. The reaction mixture was washed with HCl (1M, 100 ml), $NaHCO_3$ (aq, saturated, 100 ml) and water (100 ml) and dried ($MgSO_4$). The solvent was evaporated and gave 11.88 g (96.2 %) of the title product.
^{1}H NMR (60 MHz, $CDCl_3$): δ 4.48 (m, 4H, OCH_2CH_2O), 5.75 (s, 4H, OCH_2Cl).

w) Acetoxymethyl chloroformate

(i) O-Acetoxymethyl S-ethyl carbonothioate.

O-Chloromethyl S-ethyl carbonothioate[1] (4.50 g, 0.028 mol) in DMF (20 ml) was added to a solution of potassium acetate (2.74 g, 0.028 mol) in THF (100 ml). 18-crown-6 (0.22 g, 0.84 mmol) was then added and the reaction mixture was left with stirring at room temperature for 3 days. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silicagel, chloroform) to give 4.23 g (85%) of the title product.
^{1}H NMR (60 MHz, $CDCl_3$): δ 1.30 (t, 3H, $C\underline{H}_3CH_2$), 2.20 (s, 3H, CH_3C=O), 2.95 (q, 2H, $C\underline{H}_2CH_3$), 5.80 (s, 2H, OCH_2O).

(ii) Acetoxymethyl chloroformate

SO_2Cl_2 (2.43 g, 0.018 mol) was added to O-Acetoxymethyl S-ethyl carbonothioate (Example 1w(i), 3.15 g, 0.018 mol) at 0-5 °C with stirring during 15 min. followed by stirring at room temperature for 45 min. Evaporation of EtSCl at room temperature and 11 mmHg gave a colourless liquid. Yield: 2.44g (89 %).

^1H NMR (60 MHz, $CDCl_3$): δ 2.20 (s, 3H, $CH_3C=O$), 5.76 (s, 2H, OCH_2O).

x) Hexamethylene di(chloromethyl carbonate)

Chloromethyl chloroformate (19.12 g, 148.5 mmol) was added to an ice-cooled (0°C) solution of 1,6-hexanediol (5.90 g, 50 mmol) in CH_2Cl_2 (200 ml). Pyridine (8.70 g, 110 mmol) was then added and the reaction mixture was left with stirring for 15 min. at 0°C and 5 hours at room temperature. The reaction mixture was washed with HCl (1M, 100 ml), $NaHCO_3$ (aq, saturated, 100 ml), water (100 ml) and dried ($MgSO_4$). The solvent was evaporated and gave 13.25 g (95 %) of the title product.

^1H NMR (60 MHz, $CDCl_3$): δ 1.20-2.00 (m, 8H, $(CH_2)_4$), 4.22 (t, 4H, 2 X (CH_2O), 5.73 (s, 4H, 2 X OCH_2Cl).

y) Methacryloyloxymethyl acetate

Potassium tert. butoxide (5.0 g, 0.045 mol) was added to a solution of methacrylic acid (3.87 g, 0.045 mol) in DMF (150 ml). Chloromethyl acetate[3] (4.86 g, 0.045 mol) was added to the resulting suspension. 18-crown-6 (0.9 g, 3.45 mmol) was then added and the reaction mixture was left with stirring at room temperature for 4 days.The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (100 ml) and washed with saturated aqueous sodium hydrogen carbonate (50 ml) and water (50 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced

pressure. Flash chromatography gave 5.19 g (75 %) of the title product.

^{1}H NMR (60 MHz, $CDCl_3$): δ 2.00 (s, 3H, CH_3C=), 2.18 (s, 3H, CH_3C=O), 5.70 (m, 1H, CH_2=), 5.85 (s, 2H, -OCH_2O-), 6.25 (m, 1H, CH_2=)

z) Butyl acryloyloxymethyl carbonate

Potassium tert. butoxide (5.84 g, 0.052 mol) was added to a solution of acrylic acid (4.47 g, 0.045 mol) in DMF (220 ml). Butyl chloromethyl carbonate (Example 1i, 6.5 g, 0.052 mol) in DMF (150 ml) was added to the resulting suspension. 18-crown-6 (0.6 g) was then added and the reaction mixture was left with stirring at room temperature for 2 days.The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (100 ml) and washed with saturated aqueous sodium hydrogen carbonate (50 ml) and water (50 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography gave 4.57 g of the title product.

^{1}H NMR (60 MHz, $CDCl_3$): δ 0.80 (t, 3H, $C\underline{H}_3CH_2$), 1.28 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 4.15 (t, CH_2O), 5.78 (s, 2H, OCH_2O), 5.88 (dd, 1H, CH_2=), 6.1 (dd, 1H, CH_2=), 6.45 (dd, 1H, CH_2=C$\underline{H}$-).

aa) 3,6,9-Trioxaundecanedioic acid dichloride

3,6,9-Trioxaundecanedioic acid (2,0 mmol) was refluxed in thionyl chloride (1 ml) for 6 hours before excess thionyl chloride was evaporated under reduced pressure. The crude product was used in the subsequent step without purification.

^{1}H NMR ($CDCl_3$): δ 3.64-3.68 (m, 4H), 3.76-3.82 (m, 4H), 4.49-4.51 (m, 4H).

^{13}C NMR ($CDCl_3$): δ 70.70, 71.29, 76.65, 172.03.

ab) 1-(7-Benzyloxycarbonylheptanoyloxy)ethyl decyl carbonate

(i) 1-Benzylnonanedioic acid

A solution of nonanedioic acid (25.0 g, 0.13 mol) in benzene (550 ml) was added to p-toluenesulphonic acid (0.71 g, 3.72 mmol) and heated to 80°C. Benzyl alcohol (14.3 g, 0.13 mol) in benzene (50 ml) was added dropwise. The reaction mixture was refluxed overnight. Water was removed from the reaction mixture and collected by a Dean Stark trap. After 24 hours no benzyl alcohol was detected by TLC. The reaction mixture was cooled to room temperature and then in an ice bath. The precipated unreacted nonanedioic acid was removed by filtration. The filtrate was concentrated to dryness. The residue was purified by column chromatography using dichloromethane/ methanol (10:1) as eluent.

Yield: 28%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.31 (m, Ar); 5.10 (s, $ArCH_2$); 2.33 (t, CH_2CO); 1.62 (m, CH_2CH_2CO); 1.29 [m, $(CH_2)_3$].

(ii) Cesium 1-benzylnonanedioate

1-Benzylnonanedioic acid (Example 1ac(i), 6.3 g, 21.6 mmol) was suspended in distilled water (100 ml) and heated to 50°C. Cesium carbonate (3.5 g, 10.8 mmol) in water (20 ml) was added dropwise to pH 7. Water was removed by lyophilization for 2 days.

Yield: 95%.

(iii) 1-Chloroethyl decyl carbonate

To a stirred solution of decanol (6.0 g, 7.23 mmol) in dichloromethane (150 ml) was added dry pyridine (3.66 ml, 45.6 mmol). The solution was cooled in an ice bath. To this was added 1-chloroethyl chloroformate (6.5 g, 45.6 mmol) dropwise. The reaction mixture was allowed to proceed overnight, diluted with dichloromethane and washed

with 0.5 N HCl solution, twice with a saturated sodium bicarbonate solution and finally with distilled water. The solvent was dried over magnesium sulphate, filtered through silica and concentrated to dryness.

Yield: 93%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.43 (q, CHCl); 4.19 (t, CH_2O); 1.83 (d, $C\underline{H}_3CH$); 1.69 ($C\underline{H}_2CH_2O$); 1.40-1.22 [m, $(CH_2)_8$]; 0.88 (t, $C\underline{H}_3CH_2$).

(iv) 1-(7-Benzyloxycarbonylheptanoyloxy)ethyl decyl carbonate

Cesium 1-benzylnonanedioate (Example 1ac(ii), 5.0 g, 12.2 mmol) was dissolved in DMF (150 ml). To this was added 1-chloroethyl decyl carbonate (Example 1ac(iii), 3.25 g, 12.2 mmol), followed by potassium iodide (125 mg, 0.75 mmol). The reaction was allowed to proceed at 50°C for 3 days. The solvent was removed under reduced pressure. The residue was suspended in dichloromethane and washed 3 times with a saturated sodium bicarbonate solution and finally twice with water. After drying over magnesium sulphate the solution was evaporated to dryness. The product was purified by column chromatography using petroleum ether/ ethyl acetate (12:1) as eluent.

Yield: 65%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.31 (m, Ar); 6.78 (q, $OC\underline{H}CH_3O$); 5.10 (s, $ArC\underline{H}_2$); 4.19 (t, CH_2O); 2.33 (t, CH_2CO).

(v) 1-(7-Carboxyheptanoyloxy)ethyl decyl carbonate

To a solution of 1-(7-benzyloxycarbonylheptanoyloxy)ethyl decyl carbonate (Example 1ac(iv), 4.0 g, 7.9 mmol) in acetic acid (15 ml) was added a catalytic amount of palladium on charcoal (150 mg). The mixture was hydrogenated with H_2 at ambient temperature for 5 hours. Acetic acid was removed under reduced pressure. The residue was purified by column chromatography using n-heptane/ ethyl acetate (4:1) as eluent.

Yield: 52%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (q, OC<u>H</u>CH_3O); 4.19 (t, CH_2O); 2.32 (t, CH_2CO).
^{13}C NMR (300 MHz, DMSO-d_6) δ 174.67 (COOH); 171.30 (CH_2<u>C</u>OO); 152.68 (OCOO); 91.09 (O<u>C</u>HCH$_3$).

ac) Nonylcarbonyloxymethyl chloroformate

(i) Potassium decanoate

A solution of KOH (2.6 g, 46.4 mmol) in water (50 ml) was added dropwise to a suspension of decanoic acid (8.0 g, 46.4 mmol) in water (300 ml) at 60 °C until pH 7. Water was removed by lyophilization.
Yield: 9.28 g (95 %).

(ii) O-Nonylcarbonyloxymethyl S-ethyl carbonothioate

<u>O</u>-Chloromethyl <u>S</u>-ethyl carbonothioate[1] (4.79 g, 0.031 mol) in DMA (20 ml) was added to a suspension of potassium decanoate (Example 1ad(i), 6.5 g, 0.031 mol) in DMA (500 ml). 18-Crown-6 (0.25 g, 0.93 mmol) was then added, and the reaction mixture was left with stirring at ambient temperature for 22 hours. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/ethyl acetate (30:1)).
Yield: 5.96 g (67 %).
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H, C<u>H</u>$_3$(CH$_2$)$_8$, 1.27 (m, 12H, (CH$_2$)$_6$), 1.33 (t, 3H, <u>C</u>H$_3$CH$_2$S), 1.63 (m, 2H, C<u>H</u>$_2$CH$_2$=O), 2.37 (t, 2H, CH$_2$C=O), 2.89 (q, 2H, CH$_2$S), 5.81 (s, 2H, OCH$_2$O).
^{13}C NMR (300 MHz, $CDCl_3$): δ 14.1, 14.8, 22.7, 24.6, 25.4, 29.0, 29.2, 29.3, 29.4, 31.9, 33.9, 80.2 (OCH$_2$O), 170.7 (C=O), 172.2 (C=O).

(iii) Nonylcarbonyloxymethyl chloroformate

SO_2Cl_2 (1.17 g, 8.65 mmol) was added to <u>O</u>-nonylcarbonyloxymethyl <u>S</u>-ethyl carbonothioate (Example 1ad(ii), 2.10 g, 7.22 mmol) in CH_2Cl_2 (5 ml) at 0°C with

stirring during 15 min. followed by stirring at ambient temperature for 17 hours. Evaporation of EtSCl at 30°C and 20 mmHg gave a yellow liquid.

Yield: 1.62 g (85 %).

^{1}H NMR (300 MHZ, $CDCl_3$): δ 0.88 (t, 3H, CH_3), 1.27 (m, 12H, $(CH_2)_6$), 1.66 (m, 2H, $C\underline{H}_2CH_2C{=}O$), 2.41 (t, 2H, $CH_2C{=}O$), 5.82 (s, 2H, OCH_2O).

^{13}C NMR (300 MHz, $CDCl_3$): δ 14.1, 22.7, 24.5, 29.0, 29.19, 29.24, 29.4, 31.9, 33.8, 83.3 (OCH_2O), 150.1 ($ClC{=}O$), 171.7 ($C{=}O$).

ad) 1-Acetoxy-1-phenylmethyl vinyl carbonate

(i) 1-Chloro-1-phenylmethyl vinyl carbonate

Vinyl chloroformate (3.0 g, 0.028 mol) and benzaldehyde (4.14 g, 0.039 mol) were dissolved in 1,2-dichloroethane (30 ml) and pyridine (0.1 g, 1.28 mol) was added dropwise to the stirred solution. The solution was stirred for 1 day at 60°C, washed with water (25 ml), and the aqueous phase was back extracted with methylene chloride (25 ml). The combined organic phases were dried ($MgSO_4$) and concentrated to give 3.0 g (50%) of the title product.

^{1}H NMR (60 MHz, $CDCl_3$): δ 4.55 (dd, 1H, $CH_2{=}$), 4.95 (dd, 1H, $CH_2{=}$), 7.05 (dd, 1H, $CH_2{=}C\underline{H}{-}$), 7.25 (s, 1H, CH-Ph), 7.40 (m, 5H, Ph).

(ii) 1-Acetoxy-1-phenylmethyl vinyl carbonate

Silver acetate (2.0 g, 0.012 mol) was added to a solution of 1-chloro-1-phenylmethyl vinyl carbonate (2.50 g, 0.012 mol) in DMF (60 ml). The reaction mixture was left with stirring at room temperature for 12 hours. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silicagel, methylene chloride) to give 0.56 (20%) of the title product.

^{1}H NMR (60 MHz, $CDCl_3$): δ 2.24 (s, 3H, $CH_3C{=}O$), 4.60 (dd, 1H, $CH_2{=}$), 4.95 (dd, 1H, $CH_2{=}$), 7.00 (dd, 1H, $CH{=}$), 7.50

(m, 5H, Ph), 8.00 (s, 1H, -CH-Ph).

ae) Benzoyloxymethyl chloroformate

(i) O-Benzoyloxymethyl S-ethyl carbonothioate

O-Chloromethyl S-ethyl carbonothioate[1] (5.73 g, 0.037 mol) in DMF (20 ml) was added to a solution of potassium benzoate (5.94 g, 0.037 mol), and 18-crown-6 (0.485 g, 1.85 mmol) in DMF (130 ml) was then added and the reaction mixture was left with stirring at room temperature for 24 hours. The solvent was removed under reduced pressure. The residue was dissolved in chloroform (150 ml) and washed with water (5x20 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure, purified by flash chromatography (silicagel, chloroform) to give 7.16 g (81%) of the title product.

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.3 (t, 3H, CH_3), 2.9 (q, 2H, CH_2CH_3), 6.1 (s, 2H, OCH_2O), 7.3-7.7 (m, 3H, Ph), 8.0-8.2 (m, 2H, Ph).

(ii) Benzoyloxymethyl chloroformate

SO_2Cl_2 (4.03 g, 0.030 mol) was added to O-benzoyloxymethyl-S-ethyl carbonothioate (7.16 g, 0.030 mol) at 0-5°C with stirring during 15 min. followed by stirring at room temperature for 2 hours. Evaporation of EtSCl at room temperature and 11 mmHg gave a yellow liquid. Yield: 5.30 g (83%).

^{1}H NMR (60 MHz, $CDCl_3$): δ 6.1 (s, 2H, OCH_2O), 7.3-7.7 (m, 3H, Ph), 8.0-8.2 (m, 2H, Ph).

EXAMPLE 2 - Preparation of polymers.

a) Emulsion copolymerization of methylene dimethacrylate and styrene

50ml of a 1% wt/vol solution of sodium dodecyl sulphate in water was pre-heated to 60°C under a nitrogen atmosphere.

0.20g (1.09mmol) of methylene dimethacrylate from Example 1a above and 9.80g (0.094 mol) styrene monomer were added under vigorous stirring. The polymerisation was initiated with a metabisulphite/persulphate redox system comprising 1.6mg (7.2mmol) potassium metabisulphite and 0.08mg (0.3mmol) potassium persulphate. The polymerisation was permitted to proceed for 8 hours before cooling to room temperature. The resultant emulsion had a solids content of 11.2% which corresponded to a degree of conversion of 68%. The recovered polymer was not soluble in THF, a good solvent for polystyrene, indicating that the polymer was crosslinked.

b) Polymer from methylene bis(16-hydroxyhexadecanoate) and adipoyl chloride

A solution of adipoyl chloride (0.657 g, 3.59 mmol) in xylene/trichloroethylene (80:20 by weight, 5ml) was added dropwise to a solution of methylene bis(16-hydroxyhexadecanoate) (2.000 g, 3.59 mmol) from Example 1b(iv) above in xylene/trichloroethylene (80:20 by volume, 160 ml) at 60°C. After 44 hours at 60°C under reduced pressure, the reaction mixture was cooled to 20°C, and the solvent evaporated under reduced pressure to give 0.227 g of white solid.

IR (neat), cm^{-1}: 2915 (s), 1759, 1732 (s), 1466, 1417 (w), 1380, 1263, 1175 (w), 1105 (w), 991 (w), 798 (w), 726

^1H NMR (300 MHz, $CDCl_3$): δ 1.58 (m, 44H, CH_2), 1.63 (m, 12H, CH_2), 2.29 (m, 8H, CH_2CO), 4.04 (m, 4H, 2 X CH_2O), 5.73 (m, 2H, $-OCH_2O-$).

Size Exclusion Chromatography (SEC): Mw= 11100, Mn= 6500, Mp= 14100, Mw/Mn= 1.7

c) Polymer from methylene bis(12-hydroxydodecanoate) and adipoyl chloride

A solution of adipoyl chloride (1.22 g, 6.7 mmol) in

xylene/trichloroethylene (80:20 by weight, 5 ml) was added dropwise to a solution of methylene bis(12-hydroxydodecanoate) (3.00 g, 6.7 mmol) from Example 1c above in xylene/trichloroethylene (80:20 by volume, 100 ml) at 60°C. After 4 days at 60°C under reduced pressure, the reaction mixture was cooled to 20°C, and the solvent evaporated under reduced pressure to give a yellow solid compound. The compound was purified by flash chromatography (silica/ step gradient from chloroform to ethyl acetate).
Size Exclusion Chromatography (SEC): Mw=18276, Mn=12840, Mw/Mn=1.423

d) Polymer from methylene bis(10-hydroxydecanoate) and succinyl chloride.

Succinyl chloride (0.200 g, 1.29 mmol) was added to a solution of methylene bis(10-hydroxydecanoate) (0.500 g, 1.29 mmol) from Example 1d above in toluene (60 ml) at 70°C. After 100 hours at 70°C under reduced pressure, the reaction mixture was cooled to 20°C and solvent evaporated under reduced pressure to give 0.436 g of a yellow solid.
IR (neat): 2933 (s), 1787, 1738 (s), 1650, 1465 (w), 1413 (w), 1357 (w), 1262 (w), 1164, 1099 (w), 1049 (w), 988, 906, 802 cm^{-1}.
^1H NMR (300 MHz; $CDCl_3$): δ 1.25 (m, 20H, CH_2), 1.57 (m, 8H, CH_2), 2.32 (m, 4H, CH_2CO), 2.61 (m, 4H, CH_2CO), 4.04 (m, 4H, 2 X CH_2O), 5.70 (s, 2H, $-OCH_2O-$).
Size Exclusion Chromatography (SEC): Mw= 1870, Mn= 1580, Mp= 1310, Mw/Mn= 1.18

e) Oligomer from methylene bis(10-hydroxydecanoate) and succinic acid.

Succinic acid (0.152 g, 1.29 mmol) was added to a solution of methylene bis(10-hydroxydecanoate) (0.500 g, 1.29 mmol) from Example 1d above and p-toluene sulphonic acid (0.007

g, 0.004 mmol) in toluene (12 ml) at 130°C. After 84 hours at 140°C with continuous removal of formed water by distillation, the reaction mixture was cooled to 20°C. Solvent was evaporated under reduced pressure giving 0.425g of a yellow solid.

IR (neat): 2933 (s), 1739 (s), 1650, 1467 (w), 1415, 1360 (w), 1261, 1168, 1100, 995, 803, 724 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (m, 20H, CH_2), 1.59 (m, 8H, CH_2), 2.33 (m, 4H, CH_2CO), 2.64 (m, 4H, CH_2CO), 4.05 (m, 4H, 2 X CH_2O), 5.72 (s, 2H, $-OCH_2O-$), 10.00 (bs, 2H).

Size Exclusion Chromatography (SEC): Indicated no polymer formation (only oligomers)

f) Polymer from methylene bis(10-hydroxydecanoate) and adipoyl chloride.

A solution of adipoyl chloride (0.943 g, 5.15 mmol) in xylene/trichloroethylene (80:20 by weight, 7ml) was added dropwise to a solution of methylene bis(10-hydroxydecanoate) (2.000 g, 5.15 mmol) from Example 1d above in xylene/trichloroethylene (80:20 by volume, 120 ml) at 60°C. After 48 hours at 60°C under reduced pressure, the reaction mixture was cooled to 20°C, and the solvent evaporated under reduced pressure to give a white solid. Flash chromatography (silica, ethyl acetate) gave 0.44g of a polymer fraction.

^{1}1H NMR (300 MHz, $CDCl_3$): δ 1.32 (m, 20H, CH_2), 1.57 (m, 12H, CH_2), 2.34 (m, 8H, CH_2CO), 4.03 (m, 4H, 2 X CH_2O), 5.71 (s, 2H, $-OCH_2O-$).

Size Exclusion Chromatography (SEC): Mw= 20964, Mn= 12382, Mp= 22843, Mw/Mn= 1.693

g) Polymer from bis(chlorocarbonyloxymethyl) terephthalate and 1,6-diaminohexane.

1,6-diaminohexane (0.23 g, 0.002 mol) and triethylamine (0.40 g, 0.004 mol) in THF (5 ml) were added to a solution

of bis(chlorocarbonyloxymethyl) terephthalate (0.70 g, 0.002 mol) from Example 1e(ii) above in THF (20 ml). The reaction mixture was left with stirring for 6 days at room temperature. The reaction mixture was filtered and the solvent was removed under reduced pressure and gave a polymer which was insoluble in chloroform.
^{1}H NMR (60 MHz, $CDCl_3$): δ 1.20 (m, 8H, 4 x CH_2), 2.85-3.20 (m, 6H, 2 x NH and 2 x CH_2N), 5.85 (s, 2H, OCH_2O), 8.00 (s, 4H, Ar).

h) Polymer from methylene bis(4-hydroxymethylbenzoate) and adipoyl chloride

A solution of adipoyl chloride (1.26 g, 6.89 mmol) in 1,1,2,2-tetrachloroethane/trichloroethylene (80:20 by weight, 5 ml) was added dropwise to a solution of methylene bis(4-hydroxymethyl benzoate) (2.18 g, 6.89 mmol) from Example 1f above in 1,1,2,2-tetrachloroethane/ trichloroethylene (80:20 by weight, 90 ml) at 60°C. After 4 days at 60°C under reduced pressure, the reaction mixture was cooled to 20°C, and the solvent evaporated under reduced pressure to give 2.82 g of a brown viscous oil. Precipitation in methanol gave 0.80 g of a yellow compound. Size Exclusion Chromatography (SEC): Mw= 3793, Mn= 2715, Mp= 2845, Mw/Mn= 1.724.
^{1}H NMR (200 MHz, CD_3COCD_3): δ 1.65 (s br, 4H, CH_2), 2.40 (s br, 4H, CH_2CO), 5.18 (s, 4H, O-CH_2-Ph), 6.25 (s, 2H, OCH_2O), 7.4-7.6 (m, 4H, Ph), 7.9-8.1 (m, 4H, Ph).

i)-m) General procedure for polymerization of methacryloyloxymethyl carbonates.

A solution of methacryloyloxymethyl carbonate (1.0 g) from Example 1 l-p above in DMF (8.0 g) was heated to 60°C and AIBN (0.005 g, 0.03 mmol) was added. After 24 hours the reaction mixture was cooled and the polymer solution added dropwise to a stirred excess of methanol (non-solvent).

The polymer was filtered and washed with methanol and water, and dried under reduced pressure.

i) Polymer from methyl methacryloyloxymethyl carbonate.

IR (KBr): 1763 (C=O, str.) cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (m, 2H, CH_2), 1.90 (m, 3H), 3.85 (s, 3H, CH_3O), 5.70 (s, 2H, OCH_2O).

^{13}C NMR (75 MHz, $CDCl_3$): δ 46.35 ($\underline{C}-CH_3$), 56.55 (CH_3O), 83.59 ($-OCH_2O-$), 154.41 (C=O), 175.50 (C=O).

Differential scanning calorimetry (DSC) indicated that Tg=59.8°C and onset decomposition temperature was 242.2°C.

Thermal mechanical analysis indicated a glass transition temperature of 59.9°C.

Size Exclusion Chromatography (SEC): Mw= 100000, Mn= 59000, Mw/Mn= 1.7.

j) Polymer from ethyl methacryloyloxymethyl carbonate.

IR (KBr): 1763 (C=O, str.) cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (m, 2H, CH_2), 1.32 (t, 3H, CH_3), 1.90 (m, 3H, CH_3), 4.25 (m, 2H, CH_2O), 5.70 (s, 2H, OCH_2O).

^{13}C NMR (75 MHz, $CDCl_3$): δ 15.77 ($-OCH_2O-$), 46.35 ($\underline{C}-CH_3$), 65.90 (CH_2O), 83.50 ($-OCH_2O-$), 153.69 (C=O), 175.80 (C=O).

Differential scanning calorimetry (DSC) indicated that Tg=35.9°C and onset decomposition temperature was 260.9°C.

Thermal mechanical analysis indicated a glass transition temperature of 31.2°C.

Size Exclusion Chromatography (SEC): Mw= 34000, Mn= 20000, Mw/Mn= 1.7.

k) Polymer from butyl methacryloyloxymethyl carbonate.

IR(KBr): 1763 (C=O) cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 3H, CH_3), 1.00 (m, 2H,

CH_2), 1.39 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 1.90 (m, 3H, CH_3), 4.20 (t, 2H, CH_2O), 5.68 (s, 2H, OCH_2O).
^{13}C NMR (75 MHz, $CDCl_3$): δ 13.54 (CH_3CH_2), 18.73 (CH_2), 30.39 (CH_2), 46.26 ($\underline{C}$-CH_3), 69.72 (CH_2O), 83.67 (-OCH_2O-), 153.86 (C=O), 175.80 (C=O).
Differential scanning calorimetry (DSC) indicated that onset decomposition temperature was 239.9°C (Tg was not observed). Thermal mechanical analysis indicated a glass transition temperature of 24.7°C. Size Exclusion Chromatography (SEC): Mw= 60000, Mn= 29000, Mw/Mn= 2.1.

l) Polymer from decyl methacryloyloxymethyl carbonate.

IR(KBr): 1763 (C=O, str.) cm^{-1}
^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 3H, CH_3), 0.90 (m, 3H, CH_2), 1.30 (m, 14H, CH_2), 1.70 (m, 2H, CH_2), 1.90 (m, 2H), 4.19 (t, 2H, CH_2O), 5.66 (s, 2H, OCH_2O).
^{13}C NMR (75 MHz, $CDCl_3$): δ 13.78 (CH_3), 22.34-31.57 (CH_2), 46.26 ($\underline{C}$-CH_3), 68.70 (CH_2O), 83.67 (-OCH_2O-), 153.55 (C=O), 175.80 (C=O).
Differential scanning calorimetry (DSC) indicated onset decomposition temperature was 232.9°C (Tg was not observed). Thermal mechanical analysis indicated a glass transition temperature of -3.3°C.
Size Exclusion Chromatography (SEC): Mw= 160000, Mn= 90000, Mw/Mn= 1.7.

m) Polymer from benzyl methacryloyloxymethyl carbonate.

IR (KBr): 3077 (Ph), 1763 (C=O, str.) cm^{-1}
^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (m, 3H, CH_3), 1.90 (m, 2H), 5.25 (s, 2H, CH_2O), 5.75 (s, 2H, OCH_2O), 6.70 (s, 5H, Ph).
^{13}C NMR (75 MHz, $CDCl_3$): δ 46.26 (-$\underline{C}$-CH_3), 68.03 (-$O\underline{C}H_2Ph$), 82.02 (-OCH_2O-), 129.45 (Ph), 153.67 (C=O), 175.80 (C=O).
Differential scanning calorimetry (DSC) indicated that Tg=31.6°C and onset decomposition temperature was 197.1°C. Thermal mechanical analysis indicated a glass transition

temperature of 32.8°C.
Size Exclusion Chromatography (SEC): Mw= 92000, Mn= 44000, Mw/Mn= 2.1.

n) Free radical solution polymerisation of benzyl methacryloyloxymethyl carbonate giving low molecular weight polymer.

A solution of benzyl methacryloyloxymethyl carbonate (0.5 g, 2.0 mmol) from Example 1p above in DMF (7.5 g) was heated to 60°C and allyl mercaptan (0.0015 g, 0.02 mmol) together with AIBN (0.0025 g, 0.015 mmol) was added. After 24 hours the reaction mixture was cooled and the polymer solution added dropwise to a stirred excess of methanol (non-solvent). The polymer was filtered and washed with methanol and water and dried under reduced pressure.
Size Exclusion Chromatography (SEC): Mw= 22000, Mn=14000.

o) Free radical polymerisation of methyl 1-methacryloyloxyethyl carbonate.

AIBN (0.005 g, 0.03 mmol) was added to a solution of methyl 1-methacryloyloxyethyl carbonate (1.0 g, 5.0 mmol) from Example 1u(ii) above in dry THF (8 g) at 60°C under a dry nitrogen atmosphere. After 24 hours the reaction mixture was cooled to 20°C, and the solvent removed under reduced pressure. The resulting polymer was dissolved in CH_2Cl_2 and reprecipitated in methanol. Methanol was separated from the polymer by filtration, resulting in a white powder.
^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (m, 3H, CH_3), 1.45 (s, 3H, CH_3CH), 1.87 (m, 2H, CH_2), 3.80 (s, 3H, CH_3O), 6.65 (bs, 1H, $CHCH_3$).
Size Exclusion Chromatography (SEC): Mw= 16033, Mn= 6641, Mp= 16192, Mw/Mn= 2.41. Differential scanning calorimetry (DSC) indicated that Tg= 57.65 °C.

p) Free radical polymerisation of ethyl 1-methacryloyloxyethyl carbonate.

AIBN (0.033 g, 0.02 mmol) was added to a solution of ethyl 1-methacryloyloxyethyl carbonate (0.504 g, 2.49 mmol) from Example 1q(ii) above in dry THF (8 ml) at 50°C under a dry nitrogen atmosphere. After 7 hours the reaction mixture was cooled to 20°C, and polymer precipitated in methanol (50 ml) and the solution filtered. The resulting polymer was dissolved in THF, reprecipitated in methanol (70 ml) and filtered, resulting in 0.138 g of a white powder.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (m, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.87 (m, 2H, CH_2), 4.15 (bs, 2H, CH_2O), 6.62 (bs, 1H, $-C\underline{H}CH_3$).

Size Exclusion Chromatography (SEC): Mw= 26500, Mn= 18600, Mp= 22000, Mw/Mn= 1.43

g) Polymer from ethyl methacryloyloxymethyl carbonate, emulsion polymerisation

A solution of sodium dodecyl sulphate (0.056 g, 0.19 mmol) in water (20.5 ml) was heated to 60°C under nitrogen atmosphere, before ethyl methacryloyloxymethyl carbonate (5.266 g, 28.00 mmol) from Example 1m above was added. The polymerisation was initiated with a potassium metabisulphite (53.4 mg, 0.24mmol)/potassium persulphate (4.38 mg, 0.02 mmol) redox system. After 16 hours at 60°C, potassium persulphate (4.38 mg, 0.02 mmol) was added, and the polymerisation is permitted to proceed for another 3 hours at 60°C and under nitrogen atmosphere before cooling to 20°C.

r) Polymer from methacryloyloxymethyl benzoate.

AIBN (0.005 g, 0.03 mmol) was added to a solution of methacryloyloxymethyl benzoate (1.00 g, 4.55 mmol) from

Example 1r above in dry THF (8 g) at 60°C under a dry nitrogen atmosphere. After 24 hours the reaction mixture was cooled to 20°C, and the solvent removed under reduced pressure. The resulting polymer was dissolved in methylene chloride and reprecipitated in methanol. Methanol was separated from the polymer by filtration, resulting in a white powder.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (m, 3H, CH_3), 1.87 (m, 2H, CH_2), 5.70 (m, 2H, $-OCH_2O-$), 7.45 (m, 3H, Ph), 8.05 (m, 2H, Ph).

Size Exclusion Chromatography (SEC): Mw= 30281, Mn= 11580, Mp=32286, Mw/Mn= 2.615.

Differential scanning calorimetry (DSC) indicated that Tg= 60.98°C.

s) Free radical polymerisation of N-(2-acetoxymethoxycarbonyloxypropyl)methacrylamide.

AIBN (0.0138 g, 0.084 mmol) was added to a solution of N-(2-acetoxymethoxy-carbonyloxypropyl)methacrylamide (0.519 g, 2 mmol) from Example 1s(ii) above in dry THF (8 ml) at 50°C under a dry nitrogen atmosphere. After 3 days the solvent was removed under reduced pressure to give 0.439 of a white powder.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.8-1.2 (m, 3H, CH_3), 1.2-1.4 (m, 3H, $CH_2-CH(\underline{CH_3})O$), 1.6-2.0 (m, 2H, CH_2), 2.1 (s, 3H, CH_3CO), 2.9-3.9 (m, 2H, $NH-\underline{CH_2}$), 4.7-5.0 (m, 1H, $CH_2\underline{CH}(CH_3)-O$), 5.8 (s, 2H, $O-CH_2-O$), 6.2-7.0 (m, 1H, NH).

Size Exclusion Chromatography (SEC): Mw=5411, Mn=2857, Mw/Mn=1.894.

Differential scanning calorimetry (DSC) indicated that Tg= 52.91°C.

t) Free radical polymerisation of N-[2-(1-acetoxyethoxycarbonyloxy)propyl]methacrylamide.

AIBN (0.0031 g, 0.189 mmol) was added to a solution of N-

[2-(1-acetoyloxyethoxycarbonyloxy)propyl]methacrylamide (1.23 g, 4.5 mmol) from Example 1t(ii) above in dry THF (18 ml) at 50°C under a dry nitrogen atmosphere. After 3 days the solvent was removed under reduced pressure. Flash chromatography (step gradient, hexane/ethyl acetate (3:4) to methanol) gave 0.96 g of a white powder.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.8-1.2 (m, 3H, CH_3), 1.2-1.4 (m, 3H, CH_2-CH($C\underline{H}_3$)O), 1.5 (d, 3H, O-CH($C\underline{H}_3$)-O), 1.6-2.0 (m, 2H, CH_2), 2.0-2.2 (s, 3H, CH_3CO), 2.9-3.9 (m, 2H, NH-$C\underline{H}_2$), 4.7-5.0 (m, 1H, $CH_2C\underline{H}(CH_3)$-O), 6.2-7.0 (m, 2H, NH+O-$C\underline{H}(CH_3)$-O).

Size Exclusion Chromatography (SEC): Mw= 1991, Mn= 1268, Mp= 2105, Mw/Mn=1.548.

Differential scanning calorimetry (DSC) indicated that Tg= 51.53°C.

u) Oligomer from ethylene di (chloromethyl carbonate) and di-potassium terephthalate.

Potassium tert. butoxide (1.62 g, 0.014 mol) was added to a solution of terephthalic acid (1.20 g, 0.0072 mol) in DMF (40 ml). Ethylene di (chloromethyl carbonate) (1.78 g, 0.0072 mol) from Example 1v above was added to the resulting suspension. 18-crown-6 (0.056 g, 0.21 mmol) was then added and the reaction mixture was left with stirring at room temperature for 2 days and at 60°C for 11 days.The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 ml) and washed with saturated aqueous sodium hydrogen carbonate (30 ml) and water (30 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to give the title product.

^{1}H NMR (60 MHz, $CDCl_3$): δ 4.48 (m, 4H, OCH_2CH_2O), 6.02 (s, 4H, OCH_2O), 8.12 (s, 4H, Ar).

Size Exclusion Chromatography (SEC): Mw= 1938, Mn= 1511, Mp=2137, Mw/Mn= 1.283.

v) Free radical emulsion homopolymerisation of benzyl methacryloyloxymethyl carbonate.

A solution of sodium dodecyl sulphate (1.6×10^{-2} g, 5.5×10^{-2} mmol) in deoxygenated water (6.0 ml) was added to a 50ml two necked round bottom flask fitted with magnetic stirring bar and condenser. To the solution, potassium metabisulphite (0.015 g, 6.7×10^{-2} mmol) dissolved in deoxygenated water (1.0 ml), and benzyl methacryloyloxymethyl carbonate (2.0 g, 8.0 mmol) from Example 1p above were added. The reaction mixture was heated to a temperature of 60°C. To the heated reaction mixture potassium persulphate (1.25×10^{-3} g, 4.6×10^{-3} mmol) was added and the reaction allowed to proceed. After approximately 5 hours the polymerisation was stopped and the polymer emulsion was added dropwise to a large excess of methanol (non-solvent). The polymer was then filtered and washed with methanol and water. This procedure was repeated a total of three times in order to purify the polymer. The polymer was then collected and dried under vacuum to remove any solvent impurities. Some of the stable emulsion was not extracted as above but saved for particle size analysis by light microscopy. The size of the emulsion particles was estimated by optical microscopy and found to be just under 1μm in diameter.

w)-z) Free radical solution copolymerisation of ethyl methacryloyloxymethyl carbonate and methacrylic acid

The monomer feed mixture consisting of ethyl methacryloyloxymethyl carbonate from Example 1m above and methacrylic acid in DMF (8.0 g) was heated to 60 °C and AIBN (0.005 g, 0.03 mol) added. After 24 hours the polymer solution was added dropwise to a stirred excess of chloroform (non-solvent), filtered and washed with more chloroform and dried under reduced pressure.

Table 3

Example 2	Methacrylic acid (g , mmol)	Ethyl methacryloyloxy methyl carbonate (g , mmol)	Molar ratio methacrylic acid : 1m
w	0.73, 8.48	0.25, 1.33	86 : 14
x	0.73, 8.48	0.17, 0.90	90 : 10
y	0.73, 8.48	0.14, 0.74	92 : 8
z	0.92, 10.7	0.08, 0.43	96 : 4

^{1}H NMR (200 MHz, $CDCl_3$): δ 10 (s, 6H, 2xCH_3), 1.27 (t, 3H, $C\underline{H}_3CH_2$), 1.90 (s, 4H, 2xCH_2), 3.52 (bs, 1H, OH), 4.2 (m, 2H, $CH_3C\underline{H}_2$), 5.72 (s, $-OCH_2O-$)

Table 4: The solubility of each of the copolymers in hot and cold water.

Example 2	Solubility (cold water)	Solubility (hot water)
w	None	None
x	None	None
y	None	Some
z	Complete *	Complete

N.B. * Complete solubilisation only after a relatively long period of time undergoing dissolution.

aa) Oligomer from hexamethylene di(chloromethyl carbonate) and di-potassium terephthalate.

Potassium tert. butoxide (7.87 g, 0.068 mol) was added to a solution of terephthalic acid (5.66 g, 0.034 mol) in DMF (200 ml). Hexamethylene di(chloromethyl carbonate) (Example 1x, 9.50 g, 0.034 mol) was added to the resulting suspension. 18-crown-6 (0.24 g, 0.82 mmol) was then added and the reaction mixture was left with stirring at room temperature for 5 hours and at 60°C for 14 days. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (100 ml) and washed with saturated aqueous sodium hydrogen carbonate (50 ml) and water (50 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to give a yellow product.

^1H NMR (60 MHz, $CDCl_3$): δ 1.25-1.90 (m, 8H, 4xCH_2), 4.20 (t, 4H, -OCH_2CH_2-), 6.00 (s, 4H, OCH_2O), 8.10 (s, 4H, Ar).
Size Exclusion Chromatography (SEC): Mw= 2987, Mn=1754, Mp=3014, Mw/Mn= 1.703.
Differential scanning calorimetry (DSC) indicated that Tg is < 20°C.

ab) Polymer from methacryloyloxymethyl acetate.

AIBN (0.005 g, 0.03 mmol) was added to a solution of methacryloyloxymethyl acetate (Example 1y, 1.00 g, 4.55 mmol) in dry THF (8 g) at 60°C under a dry nitrogen atmosphere. After 24 hours the reaction mixture was cooled to 20°C, and the solvent removed under reduced pressure. The resulting polymer was dissolved in CH_2Cl_2 and reprecipitated in methanol. Methanol was separated from the polymer by filtration, resulting in a white

powder.
Differential scanning calorimetry (DSC) indicated that Tg= 54.99 °C.
Size Exclusion Chromatography (SEC): Mw= 184678, Mn= 2446, Mp=54732, Mw/Mn= 7.56

ac) Oligomer from methylene bis(10-hydroxydecanoate) and malonyl chloride.

Malonyl chloride (0.254 g, 1.80 mmol) was added to a solution of methylene bis(10-hydroxydecanoate) (Example 1d, 0.700 g, 1.80 mmol) in xylene/trichloroethylene (80:20 by volume, 50 ml) at 60°C. After 77 hours at 60°C under reduced pressure, the reaction mixture was cooled to 20°C, and the solvent evaporated to give 0.665 g of a brown, viscous liquid.
Size Exclusion Chromatography (SEC): Mw= 2700, Mn= 2100, Mp=1600, Mw/Mn= 1.28

ad) Polymer from ethyl 1-methacryloyloxyethyl carbonate, emulsion polymerisation

A mixture of sodium dodecylsulphate (6.5 mg, 0.023 mmol) in water (2.40 ml) and potassium metabisulphite (6.3 mg, 0.028 mmol) in water (0.82 ml)was heated to 60°C under nitrogen atmosphere, before ethyl 1-methacryloyloxy-ethyl carbonate (Example 1q(ii), 0.617 g, 3.10 mmol) was added. The polymerisation was initiated by adding potassium persulphate (0.54 mg, 0.002 mmol) in water (0.25 ml). The polymerisation was permitted to proceed for 20 hours at 60°C under nitrogen atmosphere, before cooling to 20°C.

ae) Polymer from methylene bis(12-hydroxydodecanoate) and triphosgene

A solution of methylene bis(12-hydroxydodecanoate)

(Example 1c, 2.0 mmol) and triphosgene (0.67 mmol) in xylene/trichloroethylene 95:5 (2 ml) was heated at 60 °C for 36 hours at 50 mmHg and then evaporated to give a polymeric material.

af) Polymer from methylene bis(12-hydroxydodecanoate) and 3,6,9-trioxaundecanedioic acid dichloride

A solution of methylene bis(12-hydroxydodecanoate) (Example 1c, 2.0 mmol) and 3,6,9-trioxaundecanedioic acid dichloride (Example 1ab, 2.0 mmol) in xylene/trichloroethylene 95:5 (2 ml) was heated at 60 °C for 36 hours at 50 mmHg and then evaporated to give a polymeric material.

ag) Dextran 10-1-(7-carboxyheptanoyloxy)ethyl decyl carbonate

To a solution of dextran 10 (0.65 g) in dry DMSO (40 ml) was added 1-(7-carboxyheptanoyloxy)ethyl decyl carbonate (Example 1ab, 1.5 g, 36 mmol), N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide (0.83 g, 4.3 mmol) and 4-pyrrolidinopyridine (42 mg, 0.28 mmol) dissolved in dry DMSO (30 ml). After stirring at ambient temperature for 2 days the reaction mixture was diluted with water (250 ml) and dialyzed against water for 30 hours. Lyophilization of the solution yielded 1.3 g of a light yellow coloured powder. In the ^{13}C NMR spectrum, a new carbonyl signal appeared at 171.28 ppm. This was within the expected region for the ester carbonyl signal from the product. The remaining signals were in accordance with the structure of the product.

ah) Polymer from Pluronic F68 and benzoyloxymethyl chloroformate

Pluronic F68 (9.889 g, 1.191 mmol) was dissolved in

toluene (dry, 30 ml). After heating to 45°C, triethylamine (0.70 ml) was added under constant stirring. Benzyloxymethyl chloroformate (Example 1 ae(ii), 1.072 g, 5.00 mmol) dissolved in toluene (4 ml) was added dropwise, followed by further triethylamine (0.25 ml) with toluene (dry, 2.5 ml). The reaction mixture was held at 45°C for 8 hours, then at 55°C for 16 hours, then cooled and filtered. The solvent was removed under reduced pressure, and the recovered compound was dissolved in toluene and reprecipitated from n-heptane (500 ml) with stirring, giving a white powder (8.45 g). IR (KBr): 1722 (C=O)cm^{-1}.

ai) Free radical polymerisation of 1-Acetoxy-1-phenylmethyl vinyl carbonate

AIBN (0.005 g, 0.03 mol) is added to a solution of 1-acetoxy-1-phenylmethyl vinyl carbonate (Example 1 ad(ii), 1.0 g) in dry THF (8 ml) at 60°C under a dry nitrogen atmosphere. After 12 hours the solvent is removed under reduced pressure. The resulting polymer is dissolved in CH_2Cl_2 and reprecipitated in a suitable solvent. The solvent is separated from the solvent by filtration, resulting in a white powder.

aj) Free radical solution co-polymerisation of N-(2-hydroxypropyl)methacrylamide with N-(2-acetoxymethoxy-carbonyloxypropyl)methacrylamide

N-(2-hydroxypropyl)methacrylamide[3] (0.430 g, 3.0 mmol) and N-(2-acetoxymethoxy-carbonyloxypropyl)methacrylamide (Example 1s, 0.778 g, 3.0 mmol) were dissolved in tetrahydrofuran (10 ml) and heated to 55°C. AIBN (0.0207 g, 0.126 mmol) was added, and the mixture was stirred at 55°C for 3 days to give a clear jelly. This was dissolved in tetrahydrofuran and the solvent evaporated under reduced pressure to give a white powder

1.33 g.
Size Exclusion Chromatography (SEC) indicated formation of polymer.

EXAMPLE 3 - Preparation of polymer particles.

a) Particles from polymer made of methylene dimethacrylate and styrene.

A sample (13 ml) of the polymer emulsion from Example 2a above was mixed with heptane (13 ml) at room temperature. After 40 minutes the sample was lyophilised to yield the product as a white powder.

b) Particles from polymer made from methylene bis(16-hydroxyhexadecanoate) and adipoyl chloride.

6.204 g of a 4.1% wt/wt solution of polymer from Example 2b above in a mixture of xylene/trichloroethylene (90:10) was added to 25 ml of a 0.5% wt/vol solution of Pluronic® F68 in water. The mixture was vigorously shaken (by hand) for one minute and freeze dried for 16 hours. Light microscopy indicated formation of microparticles.

c) Particles from polymer made from methylene bis(16-hydroxyhexadecanoate) and adipoyl chloride.

6.204 g of a 4.1% wt/wt solution of polymer from Example 2b above in a mixture of xylene/trichloroethylene (90:10) was added to 25 ml of a 0.5% wt/vol solution of Pluronic® F68 in water. The mixture was mixed with an Ultra Turax T25 mixer at speed 20500 rpm for 40 seconds and freeze dried for 16 hours. Light microscopy indicated formation of microparticles.

d) Particles from polymer made from methylene bis(16-hydroxyhexadecanoate) and adipoyl chloride.

12.408 g of a 4.1% wt/wt solution of polymer from Example 2b above in a mixture of xylene/trichloroethylene (90:10) was added to 50 ml of a 0.5% wt/vol solution of Pluronic® F68 in water. The mixture was mixed with an Ultra Turax T25 mixer at speed 24000 rpm for 40 seconds and freeze dried for 16 hours. Light microscopy indicated formation of microparticles.

e) Particles from polymer made from methylene bis(12-hydroxydodecanoate) and adipoyl chloride.

The polymer from methylene bis(12-hydroxydodecanoate) from Example 2c above and adipoyl chloride (0.40 g) in a mixture of xylene/trichloroethylene ((10:1), 4 ml) was added to 20 ml of a 0.5 % wt/vol solution of Pluronic® F68 in water. The mixture was mixed with an Ultra Turax T25 mixer at speed 20500 rpm for 30 seconds and freeze dried (0.5 mmHg) for 16 hours. Light microscopy indicated formation of microparticles.

f) Particles from oligomer made from ethylene di(chloromethyl carbonate) and di-potassium terephthalate.

A solution of oligomer from ethylene di(chloromethyl carbonate) and di-potassium terephthalate from Example 2u above in chloroform (22.5 ml of a 4% wt/vol solution made by dissolving the polymer under careful heating) was added to 30 ml of a 0.5% wt/vol solution of Pluronic® F68 in water. The mixture was mixed with an Ultra Turax T25 mixer at speed 24000 rpm for 40 seconds and freeze dried for 16 hours. Light microscopy indicated formation of micro-particles.

g) Particles from polymer made from ethyl methacryloyloxymethyl carbonate.

A solution of polymer made from ethyl methacryloyloxymethyl carbonate from Example 2j above in chloroform (9 ml of a 10% wt/vol solution) was added to 30 ml of a 0.5% wt/vol solution of Pluronic® F68 in water. The mixture was mixed with an Ultra Turax T25 mixer at speed 24000 rpm for 40 seconds and freeze dried for 16 hours. Light microscopy indicated formation of microparticles.

h) Particles from polymer made from methyl 1-methacryloyloxyethyl carbonate.

The polymer from methyl 1-methacryloyloxyethyl carbonate (0.462 g) from Example 2o above in toluene (5 ml) was added to 20 ml of a 1.0 % wt/vol solution of Pluronic® F68 in water. The mixture was mixed with an Ultra Turax T25 mixer at speed 20500 rpm for 30 seconds and freeze dried (0.05 mmHg) for 16 hours. Light microscopy indicated formation of microparticles.

i) Particles from polymer made from methacryloyloxymethyl benzoate.

The polymer from methacryloyloxymethyl benzoate (0.45 g) from Example 2r above in a mixture of toluene/trichloroethylene ((10:1), 2 ml) was added to 20 ml of a 1.0 % wt/vol solution of Pluronic® F68 in water. The mixture was mixed with an Ultra Turax T25 mixer at speed 20500 rpm for 30 seconds and freeze dried (0.05mmHg) for 4 hours. Light microscopy indicated formation of microparticles.

j) Particles from polymer made from ethyl methacryloyloxymethyl carbonate.

The polymer emulsion was prepared according to Example 2q

above. 14.783 g of the emulsion was added to 47.305 g of toluene. The mixture was vigorously stirred for 20 hours and freeze dried in 16 hours giving 1.813 g of a white powder. Light microscopy and scanning electron microscopy indicated formation of microparticles.

k) Particles from polymer made from ethyl methacryloyloxymethyl carbonate.

The polymer emulsion was prepared according to Example 2q above. 12.7612 g of the emulsion was added to 40.836 g of chloroform. The mixture was vigorously stirred for 20 hours and freeze dried for 16 hours giving 1.496 g of a white powder. Light microscopy and scanning electron microscopy indicated formation of microparticles.

l) Particles from oligomer made from ethylene di(chloromethyl carbonate) and di-potassium terephthalate.

Oligomer from ethylene di(chloromethyl carbonate) and di-potassium terephthalate (1.0 g) from Example 2u above was dissolved in 19.0 g of liquid naphthalene at 100°C. The naphthalene solution was emulsified at 90°C into 200 ml of a water solution of polyvinyl alcohol (8.0 g, Mw = 13000 - 23000) containing Pluronic® F68 (0.2 g). The emulsifying head was an Ultra Turax T25. Then the emulsion was diluted under agitation with 500 ml of the same aqueous phase at 15°C and mixed for 8 minutes. The naphthalene droplets solidified into beads which were filtered through a 50 μm filter to separate particles greater than 50 μm. The suspension was centrifuged under 1000xg and the beads were washed with water and recentrifuged. This step was repeated twice. The beads were resuspended in 100 ml of water with 0.8 g lactose and the suspension was frozen into a block at -40°C. The block was thereafter freeze dried for 16 hours. Light microscopy indicated formation of microparticles.

m) Particles from polymer made from methylene bis(16-hydroxyhexadecanoate) and adipoyl chloride.

3 ml of a 3.37% wt/vol solution of the polymer (Example 2b) in a mixture of xylene/trichloroethylene (90:10) was added to 10 ml of a 0.5 wt% solution of Tween® 80 in water. The mixture was mixed with an Ultra Turax® T25 mixer at speed 20500 rpm for 1 minute and 30 seconds, and freeze dried for 18 hours, giving a white powder. Light microscopy indicated formation of microparticles.

n) Particles from polymer made from methylene bis(16-hydroxyhexadecanoate) and adipoyl chloride.

3 ml of a 3.37% wt/vol solution of the polymer (Example 2b) in a mixture of xylene/trichloroethylene (90:10) was added to 10 ml of a 0.5 wt% solution of Brij® 99 in water. The mixture was mixed with an Ultra Turax® T25 mixer at speed 20500 rpm for 1 minute and 30 seconds, and freeze dried for 17 hours, giving a white powder. Light microscopy indicated formation of microparticles.

o) Particles from polymer made from methylene bis(16-hydroxyhexadecanoate) and adipoyl chloride.

5.5 ml of a 1.84% wt/vol solution of the polymer (Example 2b) in a mixture of xylene/trichloroethylene (90:10) was added to 10 ml of a 0.5 wt% solution of Cremophor® RH40 in water. The mixture was mixed with an Ultra Turax® T25 mixer at speed 20500 rpm for 1 minute and 30 seconds, and freeze dried for 16 hours, giving a white powder. Light microscopy indicated formation of microparticles.

p) Particles from polymer made from methylene bis(16-hydroxyhexadecanoate) and adipoyl chloride.

5.5 ml of a 1.84% wt/vol solution of the polymer (Example

2b) in a mixture of xylene/trichlororethylene (90:10) was added to 10 ml of a 0.5 wt% solution of Kollidon® 30 in water. The mixture was mixed with an Ultra Turax® T25 mixer at speed 20500 rpm for 1 minute and 30 seconds, and freeze dried for 16 hours, giving a white powder. Light microscopy indicated formation of microparticles.

g) Particles from polymer made from methylene bis(10-hydroxydecanoate) and adipoyl chloride.

4 ml of a 2.52% wt/vol solution of the polymer (Example 2f) in a mixture of xylene/trichloroethylene (90:10) was added to 10 ml of a 0.5 wt% solution of Pluronic® F68 in water. The mixture was mixed with an Ultra Turax® T25 mixer at speed 20500 rpm for 1 minute and 30 seconds, and freeze dried for 15 hours, giving a white powder. Light microscopy indicated formation of microparticles.

r) Particles from oligomer from hexamethylene di(chloromethyl carbonate) and di-potassium terephthalate.

22.5 ml of a 4% wt/vol solution of the polymer (Example 2aa) in chloroform was added to 30 ml of a 0.5 wt% solution of Pluronic® F68 in water. The mixture was mixed with an Ultra Turax® T25 mixer at speed 24000 rpm for 40 seconds, and freeze dried for 16 hours, giving a yellow, rubbery solid. Light microscopy indicated formation of microparticles.

s) Particles from polymer made from N-[2-(1-acetoxyethoxycarbonyloxy)propyl] methacrylamide.

8 ml of a 2.55% wt/vol solution of the polymer (Example 2t) in xylene/trichloroethylene (90:10) was added to 20 ml of a 0.5 wt% solution of Pluronic® F68 in water. The mixture was mixed with an Ultra Turax® T25 mixer at speed 20500 rpm for 1 minute and 30 seconds, and freeze dried

for 16 hours, giving a white powder. Light microscopy indicated formation of microparticles.

t) Particles from polymer made from methacryloyloxymethyl acetate.

8 ml of a 2.48% wt/vol solution of the polymer (Example 2ab) in xylene/trichloroethylene (90:10) was added to 20 ml of a 0.5 wt% solution of Pluronic® F68 in water. The mixture was mixed with an Ultra Turax® T25 mixer at speed 20500 rpm for 1 minute and 30 seconds, and freeze dried for 16 hours, giving a white powder. Light microscopy indicated formation of microparticles.

u) Particles from polymer made from N-(2-acetoyloxymethoxycarbonyloxypropyl) methacrylamide.

4 ml of a 2.54% wt/vol solution of the polymer (Example 2s) in chloroform was added to 10 ml of a 0.5 wt% solution of Pluronic® F68 in water. The mixture was mixed with an Ultra Turax® T25 mixer at speed 24000 rpm for 50 seconds, and freeze dried for 16 hours, giving a white powder. Light microscopy indicated formation of microparticles.

v) Particles from polymer made from ethyl 1-methacryloyloxyethyl carbonate

The polymer emulsion was prepared according to emulsion polymerisation of polymer from ethyl 1-methacryloyloxy-ethyl carbonate (Example 2ad). 2.00 g of the emulsion was added to 7.41 g of toluene. The mixture was vigorously stirred for 20 hours and freeze dried in 16 hours giving 0.250 g of a white powder. Light microscopy indicated formation of microparticles.

w) Particles from polymer made from ethyl 1-methacryloyloxyethyl carbonate

The polymer emulsion was prepared according to emulsion polymerisation of polymer from ethyl 1-methacryloyloxy-ethyl carbonate (Example 2ad). 2.00 g of the emulsion was added to 6.40 g of chloroform. The mixture was vigorously stirred for 20 hours and freeze dried in 16 hours giving 0.250 g of a white powder. Light microscopy indicated formation of microparticles.

x) Particles from polymer made from butyl methacryloyloxymethyl carbonate.

The polymer from butyl methacryloyloxymethyl carbonate (Example 2k, 0.45 g) was dissolved in toluene (9 ml). Water (30 ml) containing 0.3g Pluronic® F68 was added and an emulsion was made using an Ystral® homogenizer at 2000 rpm for 30 seconds. The emulsion was freeze dried for 19 hours and light microscopy indicated formation of microparticles.

y) HSA-coated particles from the polymer made from methacryloyloxymethyl benzoate.

The polymer made from methacryloyloxy methyl benzoate (Example 2r, 0.9 g) was dissolved in toluene (9 ml). An aqueous solution of 5% human serum albumin (HSA - 30 ml) was added and the mixture homogenized using an Ystral® homogenizer at 20000 rpm for 30 s. The resulting emulsion was freeze dried for 16 hours. Light microscopy indicated formation of microparticles.

z) Polyoxyethylene - coated particles from the polymer made from methacryloyloxy methyl benzoate.

A di-block copolymer consisting of one block polymethyl

methacrylate (Mw≈1000) and one block polyoxyethylene (POE, Mw≈2000) (0.4 g) was dissolved in toluene (9 ml). The polymer made from methacryloyloxymethyl benzoate (Example 2r, 0.9 g) was then dissolved in the toluene solution. 30 ml water was added and the mixture was homogenized using an Ystral® homogenizer at 20000 rpm for 30 seconds. The resulting emulsion was freeze dried for 16 hours yielding POE-coated microparticles.

aa) Particles from polymer made from methyl methacryloyloxymethyl carbonate

The polymer made from methyl methacryloyloxymethyl carbonate (Example 2o, 0.9g) was dissolved in toluene (9 ml). A mixture of sodium dodecylsulphate (0.3g) and Pluronic® F68 (0.025 g) in water (35 ml) was added and the solution was homogenized using an Ystral® homogenizer at 20000 rpm for 30 seconds. The emulsion was freeze dried for 16 hours and light microscopy indicated formation of microparticles.

ab) Particles from polymer made from methylene bis (12-hydroxydodecanoate) and 3,6,9-trioxaunedecanedioic acid dichloride.

The polymer made from methylene bis (12-hydroxydodecanoate) and 3,6,9-trioxaunedecanedioic acid dichloride (Example 2af , 0.9 g) was dissolved in toluene (9ml). Water (30 ml) containing Pluronic® F68 (0.3 g) was added and the mixture homogenized for 30 seconds using an Ystral® homogenizer at 20000 rpm. The emulsion was freeze dried for 48 hours. Light microscopy indicated formation of microparticles.

ac) Particles from spray drying of polymer from methacryloyloxymethyl benzoate.

0.72g of the polymer from Example 2r above was dissolved in 60g dichloromethane. The solution was spray dried in a Büchi 190 mini spray dryer. The inlet temperature was set to 54°C, and the outlet temperature was measured as 40°C. Light microscopy indicated formation of microparticles.

ad) Pluronic® F68 coated particles obtained from spray drying of polymer made from methylene bis(16-hydroxyhexadecanoate) and adipoyl chloride.

1.71g of a mixture of the polymer from Example 2b above and Pluronic® F68 (50:50) was dissolved in 100 ml dichloromethane. The solution was spray dried in a Büchi 190 mini spray drier. The inlet temperature was set to 50°C, and the outlet temperature was measured as 42°C. Light microscopy indicated formation of microparticles.

ae) Coating of particles made of polymer from methylene bis(16-hydroxyhexadecanoate) and adipoyl chloride.

Particles prepared according to Example 3c above were redispersed in several aqueous solutions of different coating materials and at different concentrations, as shown in Table 5. Light microscopy indicated an improved dispersion with reduced tendency of aggregation.

Table 5

Coating material	Concentration [% (wt/wt)]
Tween® 60	0.1, 0.5
Sodium Hexadecanoate	0.1, 0.5
Cetyl trimethyl ammonium chloride	0.1, 0.5
Kollidon® 30 (Polyvinyl pyrrolidone)	0.2, 1.0
Cremophor® RH40	0.2, 1.0
Pluronic® F68	1.0

af) Pluronic® F68 coated particles from polymer from methyl methacryloyloxymethyl carbonate

The polymer from methyl methacryloyloxymethyl carbonate (Example 2i, 0.9g) is dissolved in toluene (9 ml). Water (30 ml) containing cetyl trimethyl ammonium chloride (0.4g) is added, and the mixture homogenized using an Ystral® homogenizer. The emulsion is freeze dried for 24 hours. The obtained particles are washed several times with distilled water in order to remove the surfactant. After the last washing, the particles are freeze dried for 24 hours.

EXAMPLE 4 - Acoustic characterizations.
General procedure:

The dry powders of polymer particles prepared according to Example 3 above were redispersed in an aqueous solvent by shaking on a laboratory shaker for 12 - 16 hours. Examination by light microscopy indicated formation of

particle dispersions. The particles floated readily, as expected for gas containing particles.

The acoustic effect of the suspensions above was obtained by measuring the ultrasonic transmission through suspensions of different concentrations (mg/ml) in an aqueous carrier liquid, using a 3.5 MHz broadband transducer in a pulse-reflection technique. Pure carrier liquid was used as reference, and measurements were performed along a dilution line where the starting suspension was successively diluted with the carrier liquid. Measurements were done until the signal was reduced to approximately 3 - 5 db/cm. The obtained acoustic effects were at a level such that the products can be expected to be useful as ultrasound contrast agents. According to theoretical considerations, solid (as opposite to gas containing) particles of the same size and at the same dilutions should give an acoustic attenuation of less than 0.1 db/cm.

a) Characterization of particles from polymer made from copolymerization of methylene dimethacrylate and styrene.

The particles were from a polymer made from copolymerization of methylene dimethacrylate and styrene. The product showed a strong effect on the acoustic transmission, decreasing with increasing dilution volume, as can be seen in Fig. 1 in the accompanying drawing.

b - i) Characterization of various polymer particles

The results are summarized in Table 6 and Fig. 2-9 in the accompanying drawings.

Table 6

Acoustic measurements of particles from Example 3 above. The acoustic measurements are given in column 3 as the

concentration where the contrast effect was measured as 8 db/cm, i.e half value of saturated signal. At higher concentrations, the signal intensity increased until saturation was observed.

Example 4	Particles, Example 3, aq. medium.	Particle conc. [mg/ml] at 8 db/cm	Figure no. in acc. drawings.
b	b , 0.9 % (wt/wt) NaCl(aq)	0.9	2
c	c , 0.9 % (wt/wt) NaCl(aq)	0.2	3
d	d , 0.9 % (wt/wt) NaCl(aq)	0.5	4
e	h , Water	1.0	5
f	i , Water	0.9	6
g	y , Water	0.1	7
h	z , Water	0.5	8
i	ac , HSA/Water	2.5	9

EXAMPLE 5 - In-vivo characterization
General procedure:

Dry powder of polymer particles described in Example 3 were redispersed in a sterile 0.9% (wt/wt) NaCl (aq) solution by shaking on a laboratory shaker for 12 - 16 hours. The dispersions were injected in chinchilla rabbits, and measured by using a doppler technique where an ultrasound probe was placed directly on a carotid artery and the inferior caval vein. The particle dispersions were injected in an ear vein. Signal height and duration were recorded. The obtained signal heights were significant, indicating a strong in vivo ultrasound contrast effect for the dispersions. The long duration of the signal reveals that the in vivo stability is good.

Table 7.
In vivo characterization of polymer particles. The doses are in µg particles per kg body weight. The signal intensity is measured in doppler units [DU].

Example 5	Particles Example 3	Conc. [mg/ml]	Dose [µg/kg]	Artery		Vein	
				Peak [DU]	Duration [s]	Peak [DU]	Duration [s]
a	b	4.8	320	0.5			
b (i)	c	4.6	307	1.9	6	0.8	
b (ii)	c	4.6	767	5.6	39	2.8	
c	d	3.7	247	0.6			
d (i)	i	2.1	139	1.7	5		
d (ii)	i	2.1	347	3.2	13	1.2	70
d (iii)	i	2.1	693	3.1	10	2.1	120
e (i)	h	2.0	136	0.5			
e (ii)	h	2.0	340	1.0	5		
e (iii)	h	2.0	680	1.4	5	0.7	
f(i)	y	2.1	140	2.8	8	0.5	
f(ii)	y	2.1	350	3.7	11	0.8	44
f(iii)	y	2.1	700	5.3	33	0.8	74
g(i)	z	2.0	133	1.6	7	0	
g(ii)	z	2.0	333	3.6	32	0.7	74
g(iii)	z	2.0	666	5.3	79	1.6	99

EXAMPLE 6 - Biodegradation Studies

a) Enzyme-catalyzed hydrolysis of polymer from methacryloyloxymethyl benzoate

50 mg samples of the polymer (Example 2r), as finely divided powder, and 20ml 0.9% aqueous NaCl were added to each of three reaction vials. To one of the vials was also added 0.1 ml esterase from porcine liver in 3.2 M $(NH_4)_2SO_4$ (Sigma E-3128, 250U). To another of the vials was added 0.1 ml 3.2 M $(NH_4)_2SO_4$. Using a pH-stat (Radiometer), the pH within each of the vials was kept constant at 8.0 by adding 0.1 M NaOH. By recording the consumption of NaOH, the rates of hydrolysis were calculated. Over 45 hours at 37°C, the hydrolysis of the polymer with esterase was found to be 11 times faster than the control with $(NH_4)_2SO_4$ without esterase. In the control containing polymer in 0.9% NaCl no hydrolysis was found (see Fig. 10).

Table 8

Consumption of 0.1 M NaOH in vial containing polymer and esterase with 0.1 ml 3.2 M $(NH_4)_2SO_4$ in 20 ml 0.9% NaCl-solution (see plot (a) of Fig. 10):

Time (min)	pH	Volume 0.1 M NaOH added (ml)
0	8.00	0.000
100	8.00	0.080
220	8.00	0.142
355	8.00	0.239
2670	8.00	1.101
2710	8.00	1.105

Table 9

Consumption of 0.1 M NaOH in control containing 0.1 ml 3.2 M $(NH_4)_2SO_4$ in 20 ml 0.9% NaCl-solution (see plot (b) of Fig. 10):

Time (min)	pH	Volume 0.1 M NaOH added (ml)
0	8.00	0.000
120	8.00	0.012
240	8.00	0.030
4316	8.00	0.130

Table 10

Consumption of 0.1 M NaOH in control containing polymer in 20 ml 0.9% NaCl-solution (see plot (c) of Fig. 10):

Time (min)	pH	Volume 0.1 M NaOH added (ml)
0	8.4	0
115	8.0	0.002
250	8.0	0.002
300	8.0	0.002
1600	8.0	0.002

b) Enzyme-catalyzed hydrolysis of polymer from methylene bis(16-hydroxyhexadecanoate) and adipoyl chloride

50 mg samples of the polymer (Example 2b), as finely divided powder, and 20ml 0.9% aqueous NaCl were added to each of three reaction vials. To one of the vials was

also added 0.1 ml esterase from porcine liver in 3.2 M $(NH_4)_2SO_4$ (Sigma E-3128, 250U). To another of the vials was added 0.1 ml 3.2 M $(NH_4)_2SO_4$. Using a pH-stat (Radiometer), the pH within each of the vials was kept constant at 8.0 by adding 0.1 M NaOH. By recording the consumption of NaOH, the rates of hydrolysis were calculated. Over 44 hours at 37°C, the hydrolysis of the polymer with esterase was found to be 10 times faster than the control with $(NH_4)_2SO_4$ without esterase. In the control containing polymer in 0.9% NaCl no hydrolysis was found (see Fig. 11).

Table 11

Consumption of 0.1 M NaOH in vial containing polymer and esterase with 0.1 ml 3.2 M $(NH_4)_2SO_4$ in 20 ml 0.9% NaCl-solution (see plot (a) of Fig. 11):

Time (min)	pH	Volume 0.1 M NaOH added (ml)
0	8.00	0.000
135	8.00	0.058
255	8.00	0.134
1240	8.00	0.431
1705	8.00	0.602
2635	8.00	1.026
2665	8.00	1.034

Table 12

Consumption of 0.1 M NaOH in control containing 0.1 ml 3.2 M $(NH_4)_2SO_4$ in 20 ml 0.9% NaCl-solution (see plot (b) of Fig. 11):

Time (min)	pH	Volume 0.1 M NaOH added (ml)
0	8.00	0.000
120	8.00	0.012
240	8.00	0.030
4316	8.00	0.130

Table 13

Consumption of 0.1 M NaOH in control containing polymer in 20 ml 0.9% NaCl-solution (see plot (c) of Fig. 11):

Time (min)	pH	Volume 0.1 M NaOH added (ml)
0	8.4	0.002
50	7.9	0.002
145	7.9	0.002
235	7.9	0.002

REFERENCES:

1. Folkmann M., Lund F.J., Synthesis **1990**, 1159

2. Benneche T., Strande P., Wiggen U., Acta Chem. Scand. 43, **1988**, 74

3. Stroholm J., Kopecek J., Angew. Macromol. Chemie 70, **1978**, 109

Claims

1. A contrast agent comprising gas-containing or gas-generating polymer microparticles and/or microballoons, characterised in that the polymer is a biodegradable polymer containing units of formula (II)

$$\dagger(O)_m\text{-}CO\text{-}O\text{-}C(R^1R^2)\text{-}O\text{-}CO\text{-}(O)_n\dagger \qquad (II)$$

(wherein R^1 and R^2 each represent a hydrogen atom or a carbon-attched monovalent organic group or R^1 and R^2 together form a carbon-attached divalent organic group, and m and n, which may be the same or different, are each zero or 1).

2. A contrast agent as claimed in claim 1 wherein the polymer contains units of formula (III)

$$\dagger(O)_m\text{-}CO\text{-}O\text{-}C(R^1R^2)\text{-}O\text{-}CO\text{-}(O)_n\text{-}R^3\dagger \qquad (III)$$

(wherein m, n, R^1 and R^2 are as defined in claim 1 and R^3 is a divalent organic grouping).

3. A contrast agent as claimed in claim 2 in which R^3 is an alkylene or alkenylene group having up to 20 carbon atoms; a cycloalkylene group having up to 10 carbon atoms; an aralkylene group having up to 20 carbon atoms; an arylene group having up to 20 carbon atoms; a heterocyclic group having up to 20 carbon atoms and one or more heteroatoms selected from O, N and S; and any of the preceding groups carrying one or more functional substituents and/or interrupted in the carbon chain and/or terminated by one or more heteroatoms.

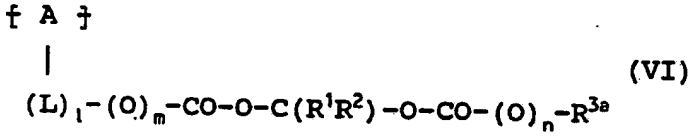
4. A contrast agent as claimed in claim 2 or claim 3 wherein R^3 is a carbon-attached divalent organic grouping.

5. A contrast agent as claimed in claim 2 wherein R^3 is a polymeric grouping.

6. A contrast agent as claimed in any of claims 2 to 5 wherein the polymer is a block or graft copolymer.

7. A contrast agent as claimed in any of the preceding claims wherein units of formula (II) crosslink polymer chains.

8. A contrast agent as claimed in claim 1 wherein the polymer is water-insoluble and contains unit of formula (VI)



$$\{A\}$$
$$(L)_l-(O)_m-CO-O-C(R^1R^2)-O-CO-(O)_n-R^{3a} \quad (VI)$$

(wherein m, n, R^1 and R^2 are as defined in claim 1; A represents a repeating unit of a non-polypeptide polymer backbone chain; L represents a linking group; l is zero or 1; and R^{3a} represents a lipophilic organic group), whereby the said lipophilic group is biodegradatively cleavable to yield a water-soluble polymer.

9. A contrast agent as claimed in claim 8 wherein the repeating units A and any comonomer units contain 1-6 carbon atoms optionally interrupted by one or more heteroatoms selected from O, N and S and/or substituted by one or more substituents comprising such heteroatoms.

10. A contrast agent as claimed in claim 9 wherein A represents ethylene or propylene.

11. A contrast agent as claimed in any of claims 8 to 10 wherein L is a C_{1-3} alkylene group optionally linked to A by and/or interrupted by one or more oxy, carbonyl, oxycarbonyl, imino or iminocarbonyl groups.

12. A contrast agent as claimed in any of claims 8 to 11 wherein the polymer is a polysaccharide.

13. A contrast agent as claimed in any of the preceding claims wherein R^1 and R^2 (when other than hydrogen) are selected from aliphatic groups having up to 10 carbon atoms, cycloalkyl groups having up to 10 carbon atoms, araliphatic groups having up to 20 carbon atoms, aryl groups having up to 20 carbon atoms, heterocyclic groups having up to 20 carbon atoms and one or more heteroatoms selected from O, N and S, and any of the preceding groups carrying one or more functional substituents.

14. A contrast agent as claimed in any of claims 8 to 13 wherein R^{3a} is an organic group as defined for R^1 and R^2 in claim 12.

15. Use of a contrast agent as claimed in any of claims 1 to 14 in diagnostic imaging.

16. Use of a contrast agent as claimed in any of claims 1 to 14 in diagnostic ultrasonic imaging.

17. Use of a contrast agent as claimed in any of claims 1 to 14 in magnetic resonance imaging.

18. A method of generating enhanced images of a human or non-human animal body which comprises administering to said body a contrast agent as claimed in any of claims 1 to 14 and generating an ultrasound or MR image of at least a part of said body.

19. A process for the preparation of a contrast agent as claimed in claim 1 which comprises incorporation of gas or a gas-generating agent into a biodegradable polymer containing units of formula (II) as defined in claim 1 so as to form polymer microparticles and/or microballoons.

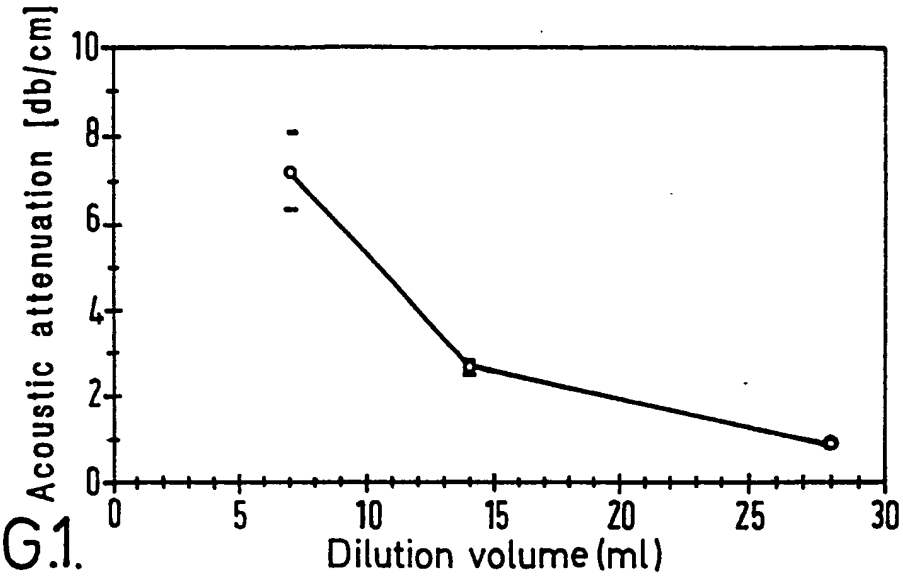

Acoustic attenuation [db/cm]
0
2
4
6
8
10
0
5
10
15
20
25
30
Dilution volume (ml)

FIG.1.

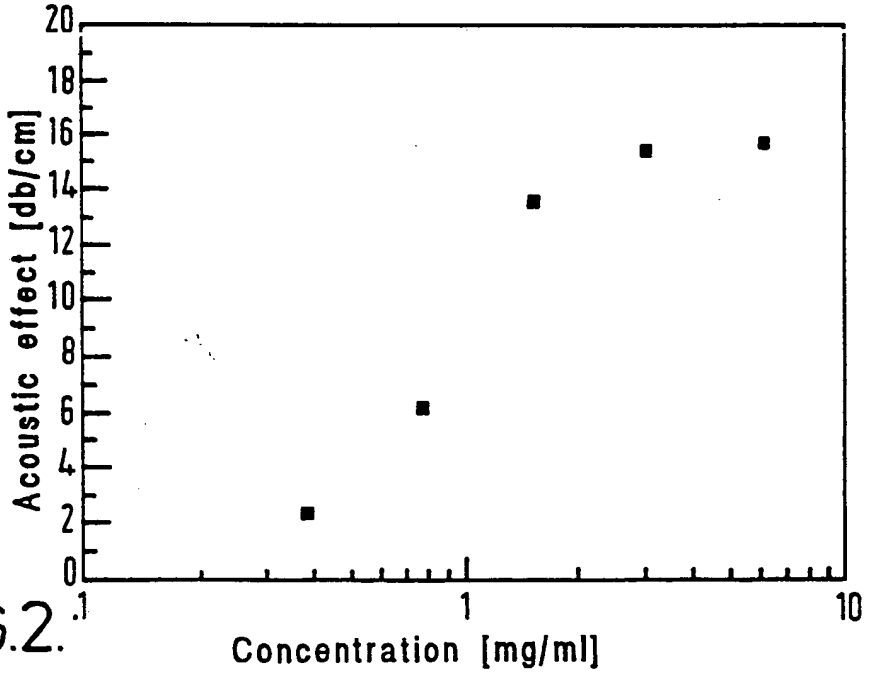

Acoustic effect [db/cm]
0
2
4
6
8
10
12
14
16
18
20
.1
1
10
Concentration [mg/ml]

FIG.2.

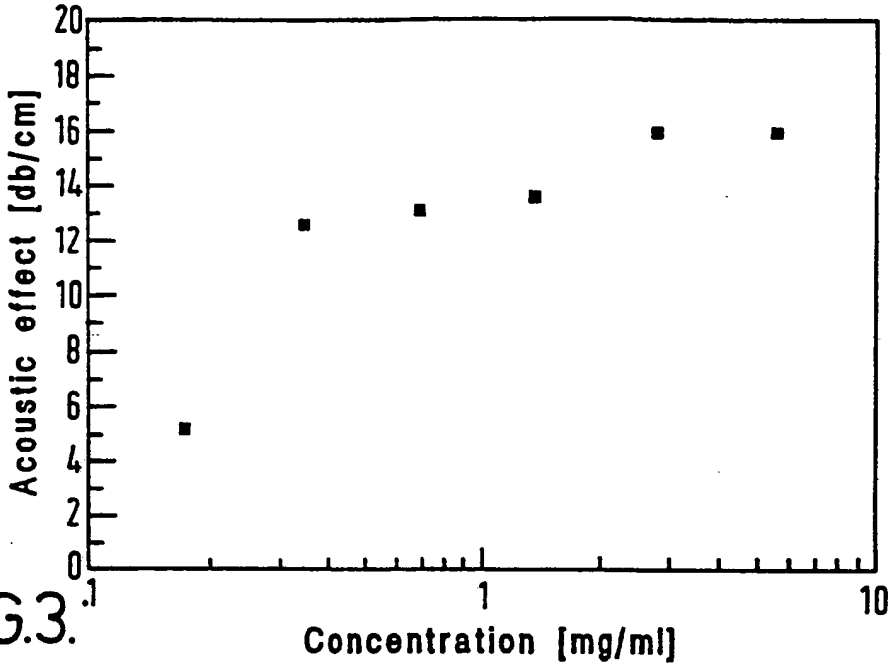

Acoustic effect [db/cm]
0
2
4
6
8
10
12
14
16
18
20
.1
1
10
Concentration [mg/ml]

FIG.3.

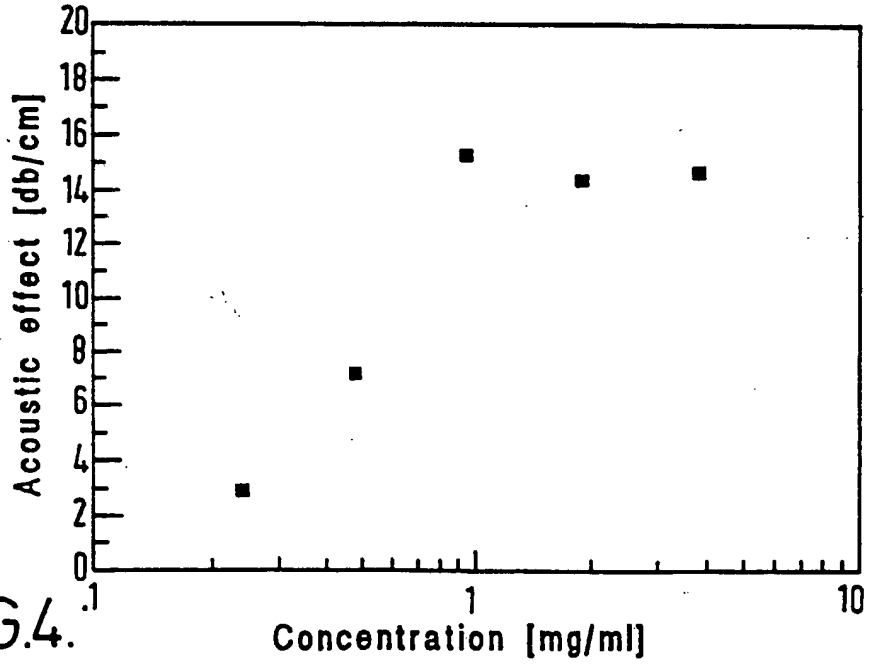

Acoustic effect [db/cm]
0
2
4
6
8
10
12
14
16
18
20
.1
1
10
Concentration [mg/ml]

FIG.4.

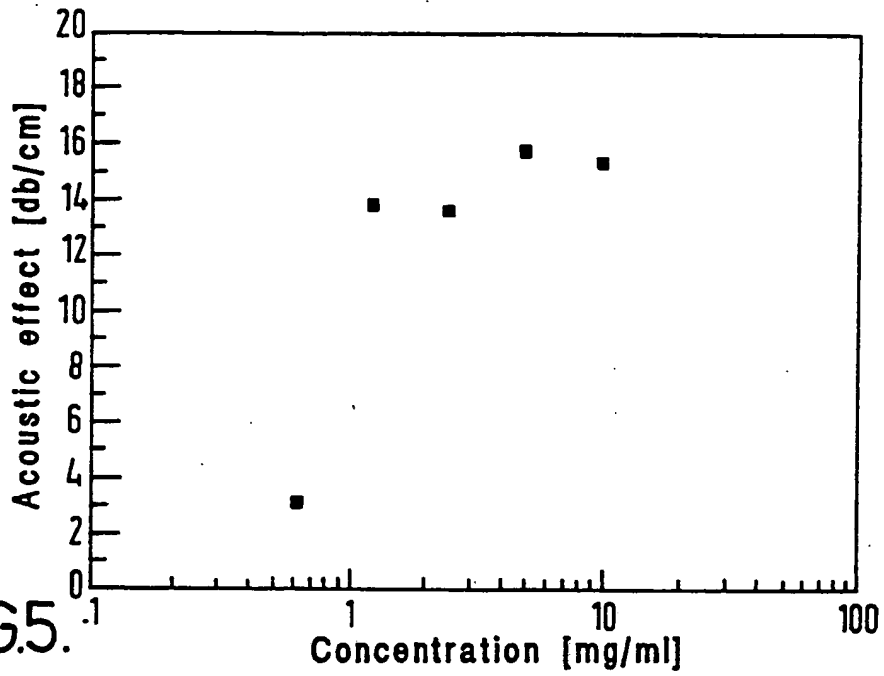

Acoustic effect [db/cm]
0
2
4
6
8
10
12
14
16
18
20
.1
1
10
100
Concentration [mg/ml]

FIG.5.

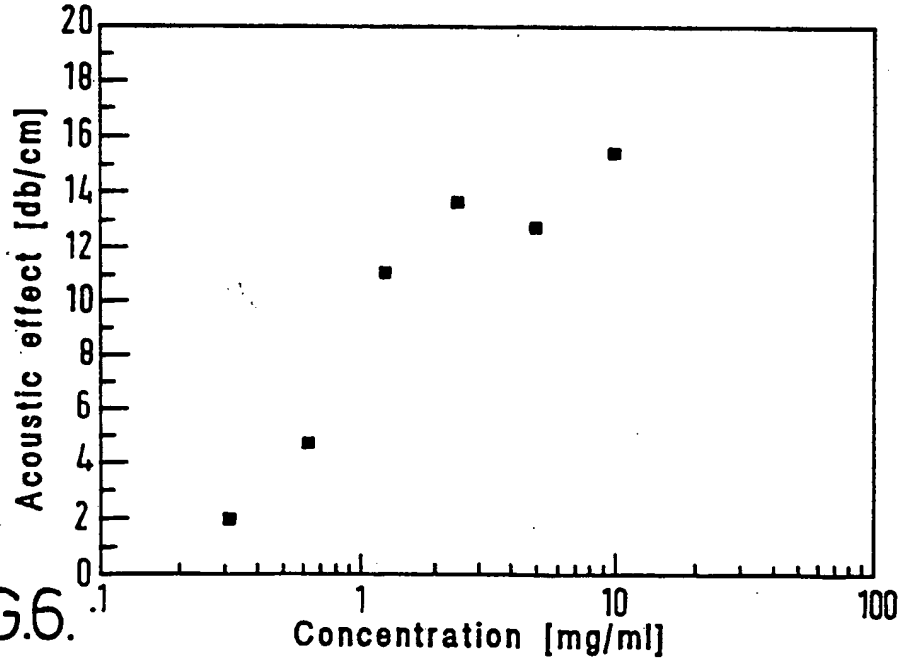

Acoustic effect [db/cm]
0
2
4
6
8
10
12
14
16
18
20
.1
1
10
100
Concentration [mg/ml]

FIG.6.

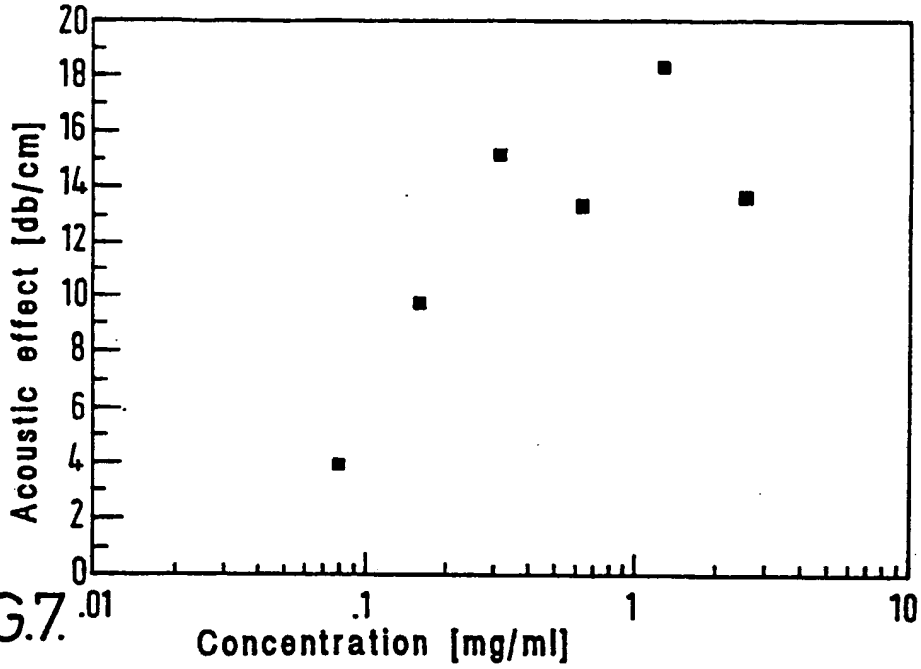

Acoustic effect [db/cm]
0
2
4
6
8
10
12
14
16
18
20
.01
.1
1
10
Concentration [mg/ml]

FIG.7.

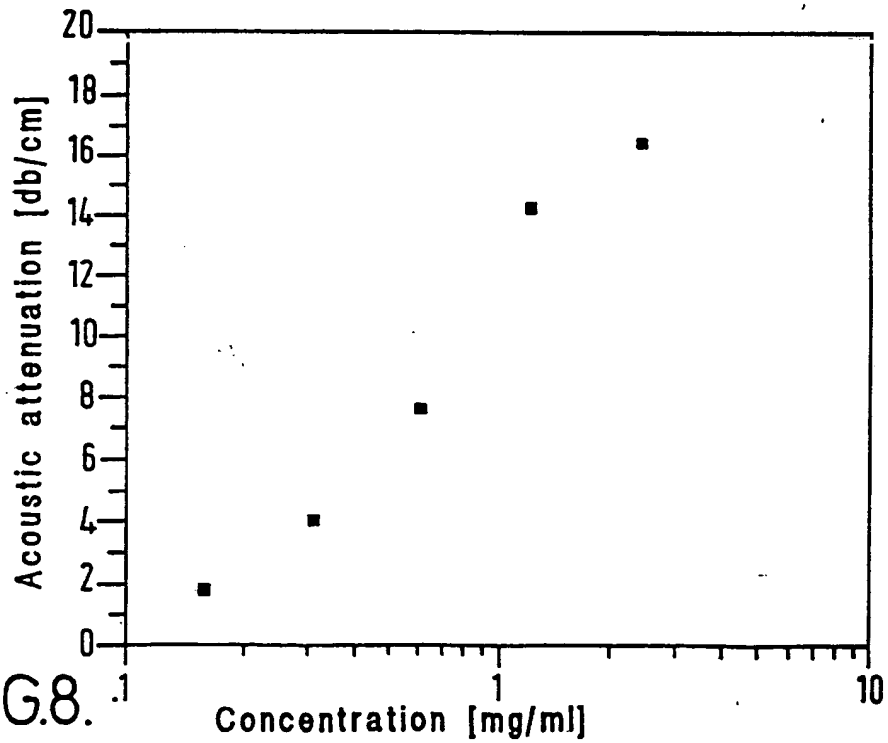
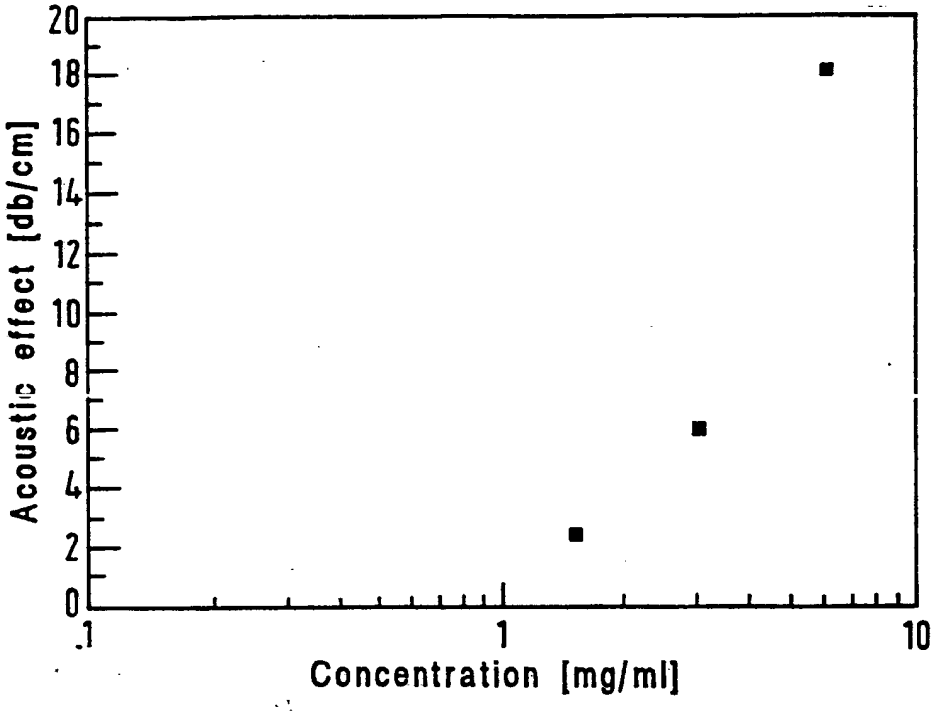

Acoustic attenuation [db/cm]
0
2
4
6
8
10
12
14
16
18
20
.1
1
10
Concentration [mg/ml]

FIG.8.

FIG.9.


20
18
16
14
12
10
8
6
4
2
0
Acoustic effect [db/cm]
.1
1
10
Concentration [mg/ml]

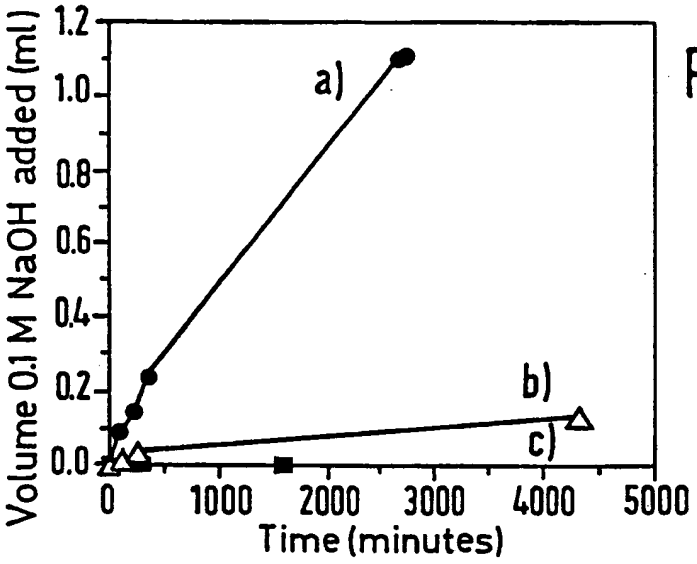

Volume 0.1 M NaOH added (ml)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
a)
b)
c)
0
1000
2000
3000
4000
5000
Time (minutes)

FIG.10.

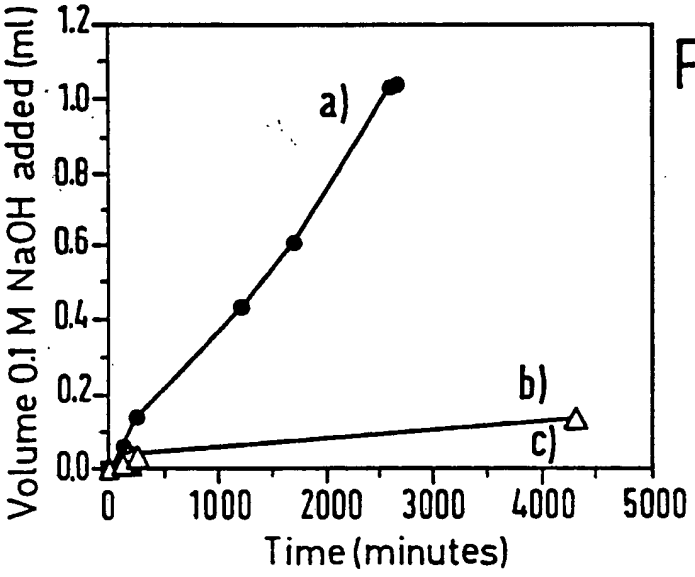

Volume 0.1 M NaOH added (ml)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
a)
b)
c)
0
1000
2000
3000
4000
5000
Time (minutes)

FIG.11.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00470

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K49/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,X	WO,A,9 204 392 (NYCOMED AS) 19 March 1992 cited in the application see page 18, line 18 - line 34; claims; examples	1-19
P,X	WO,A,9 217 213 (NYCOMED AS) 15 October 1992 see the whole document	1-2,5-6, 15-16, 18-19
X	EP,A,0 458 745 (SINTETICA) 27 November 1991 cited in the application see claims	1-16, 18-19
P,X	WO,A,9 217 212 (NYCOMED AS) 15 October 1992 see claims; examples	1-6, 18-19

-/--

[10] Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14 JULY 1993	03. 08. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	BERTE M.J.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	WO,A,9 221 382 (HOLMES J.) 10 December 1992 see claims	1-16, 18-19

INTERNATIONAL SEARCH REPORT

I.. .rnational application No.
PCT/GB93/00470

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claim 18 is directed to a method of treatment of (diagnostic method practised on) the human/animal body (Rule 39.1(IV) PCT) the search has been carried out and based on the alleged effects of the compound/COMPOSITION.

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
In view of the large number of compounds which are defined by the general formula of claims 1,2,8 the search was limited to the compounds mentioned in the description and examples.

3. [X] Claims Nos.: 17
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300470
SA 70888

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 14/07/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9204392	19-03-92	AU-A-	8525691	30-03-92
		EP-A-	0547126	23-06-93
		AU-A-	1443992	02-11-92
		WO-A-	9217436	15-10-92
WO-A-9217213	15-10-92	AU-A-	1428392	02-11-92
		AU-A-	1443992	02-11-92
		WO-A-	9217436	15-10-92
EP-A-0458745	27-11-91	AU-A-	7614491	21-11-91
		CA-A-	2042722	19-11-91
		CN-A-	1056634	04-12-91
		JP-A-	4226923	17-08-92
WO-A-9217212	15-10-92	AU-A-	1425392	02-11-92
WO-A-9221382	10-12-92	AU-A-	1929192	08-01-93